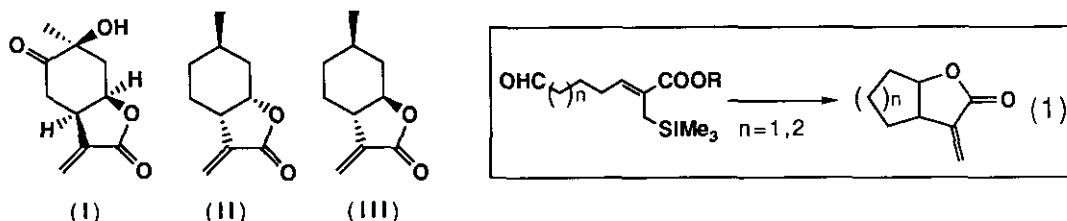


DIASTEREOSELECTIVE CYCLIZATION OF ω -FORMYLATED ALLYLSILANES INTO BICYCLIC α -METHYLENE- γ -BUTYROLACTONES; A FACILE SYNTHESIS OF *p*-MENTHANOLIDES¹

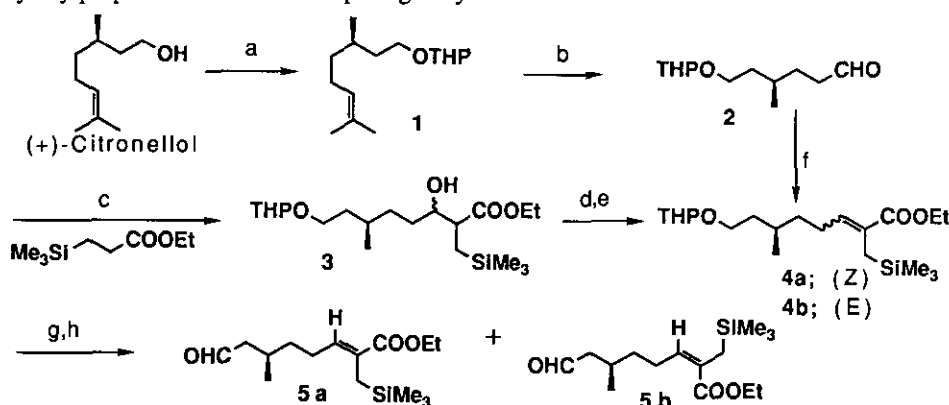
Kiyoshi Nishitani, Hiroshi Fukuda, and Koji Yamakawa*
Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya
Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Abstract- Intramolecular cyclization of ω -formylated allylsilanes, ethyl (*Z*)- and (*E*)-2-(trimethylsilyl)methyl-6(*R*)-methyl-7-formyl-hept-2-enoates (**5a** and **5b**), was effected by BF₃·etherate, giving *cis* (1*S*,2*S*,5*R*)- and *trans* (1*R*,2*S*,5*R*)-hydroxy esters (**6** and **7**) in complete diastereoselectivities. Treatment of the allylsilanes (**5a** and **5b**) with TiCl₄ predominantly gave the *cis* (1*S*,2*S*,5*R*)-isomer in excellent yields. These hydroxy esters (**6** and **7**) were easily converted into α -methylene- γ -butyrolactones, *cis*- and *trans*-*p*-menthanolides (**II** and **III**).

The moiety of α -methylene- γ -butyrolactone is an important partial structure of many naturally occurring terpenoid lactones.² The α -methylene- γ -butyrolactones fused to six-membered carbocyclic rings were found in eudesmanolide sesquiterpenoids and monoterpenoid lactones such as paeonilactone-B (**I**) isolated from paeony root (*Paeonia albiflora* PALLAS *trichocarpa* BUNGE) by Hayashi *et al.*³ We have reported a facile synthesis of α -methylene- γ -butyrolactones fused to five or six membered carbocyclic rings employing the intramolecular Hosomi reaction of ω -formylated β -alkoxycarbonylallylsilanes (eq. 1).⁴ This method will be very useful to synthesize these terpenoid lactones. For this purpose, this cyclization reaction needs a proper and high diastereoselectivity. The target molecules in this synthetic application are *cis*- and *trans*-*p*-menthanolides (**II** and **III**), which have been prepared from isopulegol.⁵ In this communication, we report a more facile synthesis of **II** and **III**, having a bicyclic α -methylene- γ -lactone function, by a highly diastereoselective intramolecular cyclization reaction of optically active formylated allylsilanes (**5a** and **5b**) derived from (+)-citronellol.



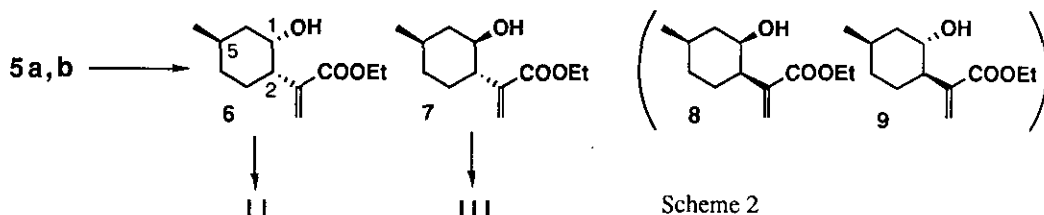
A synthesis of the optically active allylsilanes (**5a** and **5b**) starting from (+)-citronellol was as follows. Tetrahydropyranyl ether of (+)-citronellol (**1**) was treated with ozone followed by methyl sulfide to give an aldehyde (**2**) in good yield. The Horner-Emmons variant of the Wittig reaction of the aldehyde (**2**) with $(\text{EtO})_2\text{POCH}(\text{CH}_2\text{SiMe}_3)\text{COOEt}$ ⁶ afforded a mixture of (E)- and (Z)- α,β -unsaturated esters (**4a** and **4b**) in 37% yield. Removal of the protecting group followed by the Swern oxidation of the mixture yielded a mixture of aldehydes, which can be separated into (Z)- and (E)- α,β -unsaturated esters (**5a** and **5b**) by hplc in 69 and 25% yields, respectively. The geometry of the double bond of the α,β -unsaturated esters was elucidated by ¹H-nmr spectroscopy. ⁷ The (Z)-unsaturated ester (**5a**) was also selectively synthesized from the aldehyde (**2**) and ethyl β -trimethylsilylpropionate *via* several steps in good yield as shown in Scheme 1.



a: DHP, PPTS (quant.) b: O_3 Oxid./ $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (3:1) (96%) c: LDA, -78°C (96%) d: $\text{MsCl}/\text{Et}_3\text{N}$
 e: DBU/benzene, reflux (91%) f: 1) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH/DME , 2) $\text{Me}_3\text{SiCH}_2\text{I}$, 3) NaH (37%)
 g: PPTS/ EtOH (quant.) h: Swern Oxid. (94%)

Scheme 1

Intramolecular Hosomi reaction of the formylated allylsilanes (**5a** and **5b**) was effected by TiCl_4 or BF_3 -etherate in CH_2Cl_2 at a low temperature to give cyclohexanol derivatives in excellent yields. The results are summarized in Table 1. In these reactions, we obtained only two isomers [(1S,2S,5R) (**6**) and (1R,2S,5R) (**7**)] of four possible stereoisomers (**6**, **7**, **8** and **9**). ⁸ And also, we selectively obtained *cis*-hydroxy ester (**6**) by treatment of the (Z)-isomer (**5a**) with BF_3 -etherate, or the (E)-isomer with TiCl_4 . On the other hand, the *trans*- isomer (**7**) was selectively obtained from the (E)-ester (**5b**) by the use of BF_3 -etherate. The *cis*- and *trans*- hydroxy esters were quantitatively converted into *cis*- and *trans*-fused lactones (**II** and **III**), respectively. The spectral data ⁹ were coincident with those of *p*-menthanolides (**II** and **III**), ^{5a,c}



Scheme 2

TABLE I. Cyclization Reaction of **5a** and **5b**

Run	Aldehyde	Acid	Reaction conditions ^a		Product Yield (%)			Conversion Yield (%)	Ratio cis/trans
			Temp.(°C)	Time(h)	6	7	S.M.		
1	5a	TiCl ₄	-10	0.5	79	14	0	93	5.8
2			-25	2.0	66	21	0	87	3.2
3		BF ₃ ·Et ₂ O	-10	5.0	82	0	10	91	cis
4			-25	5.0	65	0	31	95	cis
5	5b	TiCl ₄	-10	0.5	69	0	0	69	cis
6			-25	0.5	88	0	0	88	cis
7		BF ₃ ·Et ₂ O	-10	5.0	0	41	15	48	trans
8			-25	5.0	0	35	27	47	trans

a) All reactions were carried out in CH₂Cl₂ with 1.1 equiv. of the Lewis acid at 0.01 M concentration of the substrate.

Now, we can easily synthesize *cis*- and *trans*-*p*-menthanolides from (+)-citronellol in fairly good yield and selectivity. The selectivity of the cyclization reaction was assumed as shown in Figure 1. The six-membered cyclic intermediate, chelating with the Lewis acids, expected to have an equatorial conformation of the ester and the methyl functions, giving *trans* relationship between these two groups. The *cis* and *trans* selectivities of the cyclization reaction have not been clear yet. However, it may be explained that the transition states (**5aC** and **5bT**) of the cyclization reaction (using BF₃-etherate) of the (*Z*)- and (*E*)-esters (**5a** and **5b**) are preferable to the transition states (**5aT** and **5bC**) owing to a steric or electronic repulsion.^{6,10} The *cis* selectivity of the cyclization reaction of both (*Z*)- and (*E*)-esters using TiCl₄ may partly suggest a transition state (**B**).¹¹ The details of the mechanisms are now being investigating.

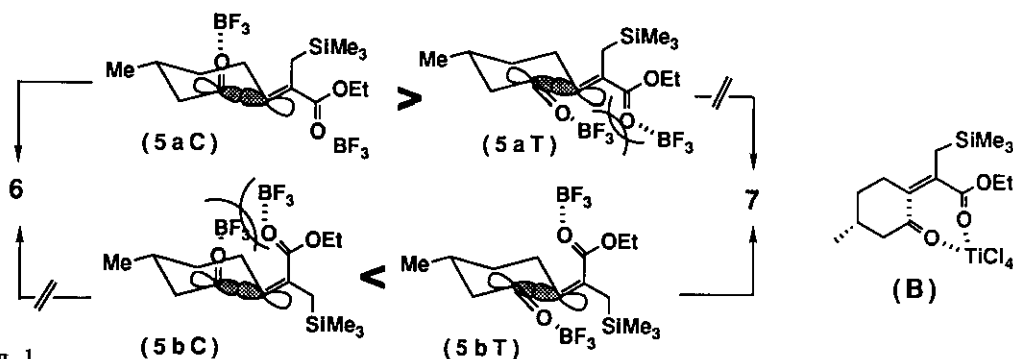


Fig. 1

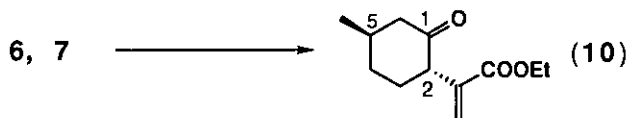
ACKNOWLEDGEMENTS

We thank Miss N. Sawabe and Mrs. F. Hasegawa of this laboratory for nmr and mass spectral measurements, and also Takasago Kouryou Co., Ltd. for providing (+)-citronellol.

REFERENCES AND NOTES

1. This paper forms part XLII of the series entitled "Studies on the Terpenoids and Related Alicyclic Compounds", Part XLI in this series, K. Nishitani, K. Harada, N. Sano, K. Sato, and K. Yamakawa, *Chem. Pharm. Bull.*, 1991, **39**, 2514.

2. N. H. Fischer, E. J. Olivier, and H. D. Fischer, *Fortschr. Chem. Org. Naturst.*, 1979, **38**, 47.
3. T. Hayashi, T. Shinbo, M. Shimizu, M. Arisawa, S. Matsuda, and T. Kikuchi, *Tetrahedron Lett.*, 1985, **26**, 3699.
4. K. Nishitani and K. Yamakawa, *Tetrahedron Lett.*, 1987, **28**, 655 ; 1991, **32**, 843.
5. a) T. J. Brocksom, R. B. dos Santos, N. A. Varanda, and U. Brocksom, *Syn. Comm.*, 1988, **18**, 1403
b) T. J. Brocksom and J. T. B. Ferreira, *ibid.*, 1981, **11**, 105, c) B. S. Bal and H. W. Pinnick, *Heterocycles*, 1981, **16**, 2091.
6. R. Henning and H. M. R. Hoffmann, *Tetrahedron Lett.*, 1982, **23**, 2305; C. Kuroda, S. Shimizu, and J. Y. Satoh, *J. Chem. Soc., Chem. Commun.*, 1987, 286.
7. Spectral data; **5a**, ir; 1730, 1710, 1640, 850 cm^{-1} , $^1\text{H-nmr}$ δ ; 6.49(1H, t, $J=7$ Hz, olefinic H), 10.72(1H, t, $J=2$ Hz, CHO); **5b**, ir; 1730, 1710, 1640, 850 cm^{-1} , $^1\text{H-nmr}$ δ ; 5.58(1H, t, $J=7$ Hz, olefinic H), 10.74(1H, t, $J=2$ Hz, CHO).
8. A procedure for the cyclization reaction; CH_2Cl_2 (30ml) solution of the aldehyde (**5a** or **5b**) (0.3 mmol) was stirred with a Lewis acid (0.33 mmol) at a low temperature monitoring by tlc. The reaction mixture was poured into aqueous 1N NaOH solution, and extracted with CH_2Cl_2 . The crude material was subjected to hplc with 10% EtOAc-hexane. The stereochemistry of the resulting hydroxy esters (**6** and **7**) was determined from the $^1\text{H-nmr}$ data, especially the splitting patterns of the C-1, 2 and 5 methine proton signals, as described below. Spectral data: **6**, ir (neat); 3450, 1710, 1630 cm^{-1} , $^1\text{H-nmr}$ (500 MHz, CDCl_3); δ 2.69(1H, br d, $J=13$ Hz, 2-H), 4.00(1H, br s), 5.61(1H, t, $J=1$ Hz, olefinic H), 6.31(1H, d, $J=1$ Hz, olefinic H). **7**, ir (neat); 3425, 1710, 1630 cm^{-1} , $^1\text{H-nmr}$ (500 MHz, CDCl_3); δ 1.54(1H, dqt, $J=3, 7, 13$ Hz, 5-H), 2.42(1H, ddd, $J=4, 10, 11$ Hz, 2-H), 3.56(1H, dt, $J=4, 11$ Hz, 1-H), 5.65(1H, s, olefinic H), 6.23(1H, d, $J=1$ Hz, olefinic H).



Oxidation of the hydroxy esters (**6** and **7**) gave the same cyclohexanone derivatives (**10**). **10**, Ir (neat); 1710, 1630 cm^{-1} , $^1\text{H-nmr}$ (500 MHz, CDCl_3); δ 3.51(1H, dd, $J=5.5, 13.5$ Hz, 2-H), 5.54, 6.34 (each 1H, s, olefinic H).

9. Spectral data; **II** (oil), $[\alpha]_D -139.3^\circ$ (CHCl_3 , $c=0.28$), ir (neat); 1770,1665,1260,1190,1125,1005, 950, 880, 815 cm^{-1} , $^1\text{H-nmr}$ (500 MHz, CDCl_3); δ 0.94(3H, d, $J=7$ Hz, 5-Me), 2.84(1H, ddd, $J=4, 5, 11$ Hz, 2-H), 4.51(1H, dt, $J=4, 4$ Hz, 1-H), 5.52, 6.10(each 1H, d, $J=1$ Hz, olefinic H). **III** (colorless needles, mp 37-39°C), $[\alpha]_D +54.4^\circ$ (CHCl_3 , $c=0.26$), ir (KBr); 1780, 1690, 1270, 1250, 1005, 950, 850, 830 cm^{-1} , $^1\text{H-nmr}$ (500 MHz, CDCl_3); δ 1.05(3H, d, $J=7$ Hz, 5-Me), 2.36(1H, ddt, $J=3, 7, 12$ Hz, 2-H), 3.74(1H, dt, $J=3, 12$ Hz, 1-H), 5.39, 6.01(each 1H, d, $J=3$ Hz, olefinic H).
10. A. Itoh, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 1978, 2461.
11. M. T. Reez, "Organotitanium Reagents in Organic Synthesis", Springer-Verlag, Berlin Heidelberg, 1986 pp. 39-42.

Received, 23rd October, 1991