DIASTEREOSELECTIVE CYCLIZATION OF ω-FORMYLATED ALLYLSILANES INTO BICYCLIC α-METHYLENE-γ-BUTYROLACTONES; A FACILE SYNTHESIS OF *p*-MENTHANOLIDES[1]

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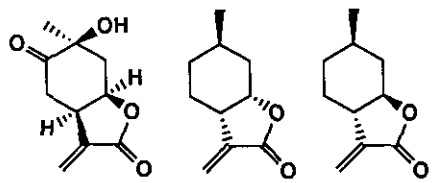
Abstract- Intramolecular cyclization of ω-formylated allylsilanes, ethyl (Z)- and (E)-2-(trimethylsilyl)methyl-6(R)-methyl-7-formyl-hept-2-enoates (**5a** and **5b**), was effected by BF_3-etherate, giving *cis* (1S,2S,5R)- and *trans* (1R,2S,5R)-hydroxy esters (**6** and **7**) in complete diastereoselectivities. Treatment of the allylsilanes (**5a** and **5b**) with $TiCl_4$ predominantly gave the *cis* (1S,2S,5R)-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**).

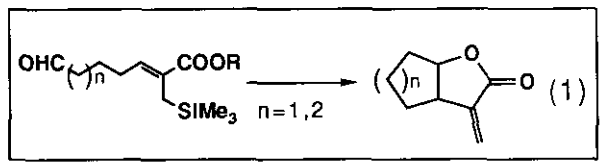
The moiety of α-methylene-γ-butyrolactone is an important partial structure of many naturally occurring terpenoid lactones.[2] The α-methylene-γ-butyrolactones fused to six-membered carbocyclic rings were found in eudesmanolide sesquiterpenoids and monoterpenoid lactones such as paeonilactone-B (**I**) 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 diastereoselectiivity. 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.



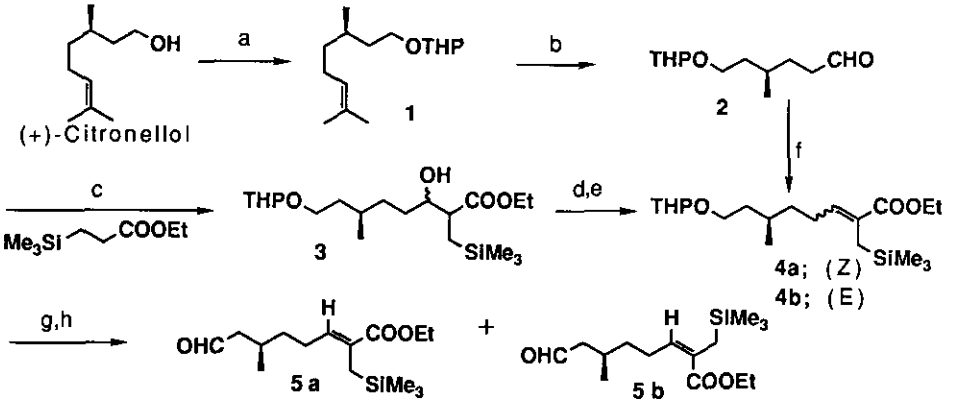
(I)

(II)

(III)



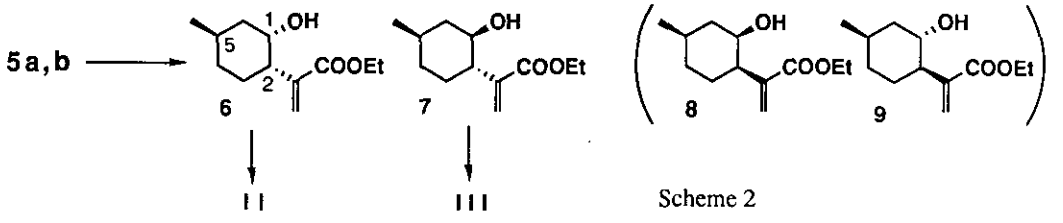
A synthesis of the optically active allylsilanes (**5a** and **5b**) starting from (+)-citronellol was as follows. Tetrahydropyranyl ether of (+)-citronellol (**1**) was treated with ozone followed by methyl sulfide to give an aldehyde (**2**) in good yield. The Honer-Emmons variant of the Wittig reaction of the aldehyde (**2**) with $(EtO)_2POCH(CH_2SiMe_3)COOEt$ [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 ^{1}H-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 Scheme1.



a: DHP,PPTS (quant.) b: O_3 Oxid./MeOH:CH_2Cl_2 (3:1) (96%) c: LDA,-78°C (96%) d: MsCl/Et_3N
e: DBU/benzene, reflux (91%) f: 1) $(EtO)_2P(O)CH_2COOEt$, NaH/DME, 2) Me_3SiCH_2I, 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·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·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	Raction conditions[a]		Product Yield (%)			Conversion Yield (%)	Ratio
			Temp.(°C)	Time(h)	**6**	**7**	**S.M.**		cis/trans
1	**5a**	$TiCl_4$	-10	0.5	79	14	0	93	5.8
2			-25	2.0	66	21	0	87	3.2
3		$BF_3{\cdot}Et_2O$	-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		$BF_3{\cdot}Et_2O$	-10	5.0	0	41	15	48	trans
8			-25	5.0	0	35	27	47	trans

a) All reactions were carried out in CH_2Cl_2 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.

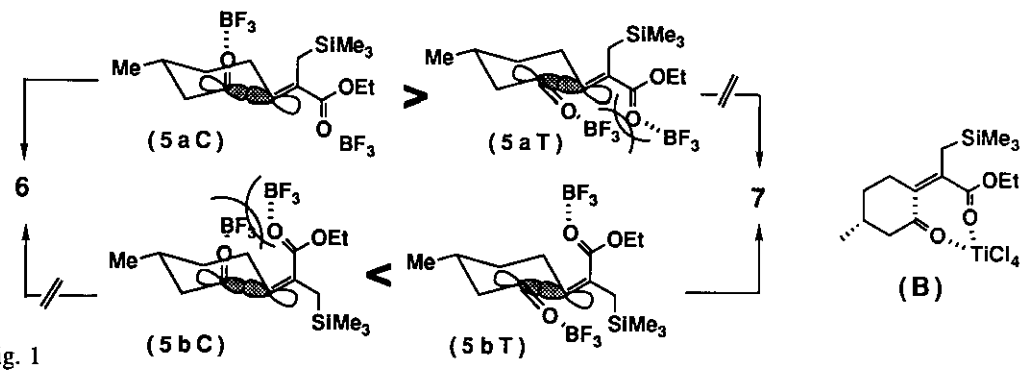


Fig. 1

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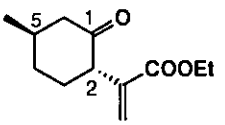
7. Spectral data; **5a**, ir; 1730, 1710, 1640, 850 cm^{-1}, ^{1}H-nmr δ; 6.49(1H, t, *J*=7 Hz, olefinic H), 10.72(1H, t, *J*=2 Hz, CHO); **5b**, ir; 1730, 1710, 1640, 850 cm^{-1}, ^{1}H-nmr δ; 5.58(1H, t, *J*=7 Hz, olefinic H), 10.74(1H, t, *J*=2 Hz, CHO).
8. A procedure for the cyclization reaction; 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}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}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}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).

6, 7 ⟶  **(10)**

Oxidation of the hydroxy esters (**6** and **7**) gave the same cyclohexanone derivatives (**10**). **10**, Ir (neat); 1710, 1630 cm^{-1}, ^{1}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° ($CHCl_3$, c=0.28), ir (neat); 1770,1665,1260,1190,1125,1005, 950, 880, 815 cm^{-1}, ^{1}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° ($CHCl_3$, c=0.26), ir (KBr); 1780, 1690, 1270, 1250, 1005, 950, 850, 830 cm^{-1}, ^{1}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).
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