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EFFICIENT STEREOSELECTIVE SYNTHESES OF BOTH (±)-JUVABIONE AND (±)-*EPI*-JUVABIONE BY NEW EXTRACYCLIC STEREOCONTROL METHODOLOGY

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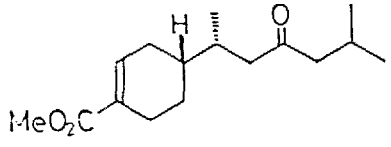
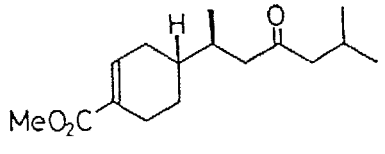
Summary: The Hosomi-Sakurai reactions of *E*- and *Z*-crotylsilanes with cyclohexenone at -78 °C showed respectively high *erythro* and relatively low *threo* selectivities, modification of the silyl substituents giving a variable effect. In the reaction with *Z*-alkoxycrotylsilanes, the *threo* selectivity could be improved by the utilization of the kinetic difference between the diastereomeric products **4** and **5** to the secondary cyclization. Starting from **4** and **5** thus obtained, the syntheses of both (±)-juvabione and (±)-*epi*-juvabione have been respectively achieved in a concise way.

Juvabione (**1**) and *epi*-juvabione (**2**) are plant constituents with potent juvenile hormone activity and are well known in that they cannot be separated *per se* and are difficult to distinguish from one another spectroscopically.[1] Among the several syntheses so far published only a few approaches are stereoselective[2-4] and all pertain to the synthesis of **2**.[2] Thus the stereoselective synthesis of juvabiones represents an intriguing challenge for extracyclic control.[5] We report here a novel method of divergent stereocontrol, the application of which led to the first practical stereoselective syntheses of both (±)-juvabione and (±)-*epi*-juvabione.

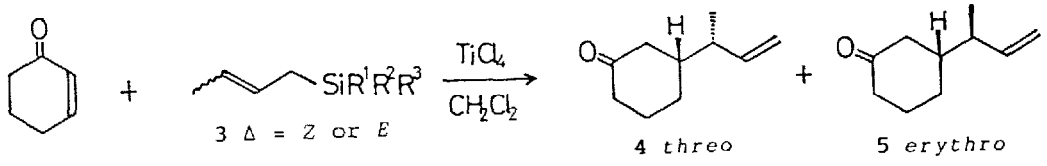


1 juvabione



2 *epi*-juvabione

Our strategy is that the diastereoselectivity in the addition reaction of crotylsilane **3** with 2-cyclohexenone might be controlled by the double bond geometry and modification of the silyl substituents in the former (Scheme 1).



3 Δ = *Z* or *E*

4 *threo* **5** *erythro*

Scheme 1

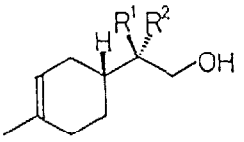
Table 1 Diastereoselectivity in the reaction cyclohexenone with crotylsilanes

Entry	Crotylsilane				Reaction conditions temp and time ($TiCl_4$, equiv.)	Diastereomer ratio **4**/**5**[a]	Yield (%)
	Olefin geometry	Silyl substituents R^1	R^2	R^3			
1	*E*	Me	Me	Me	-78°C, 1h (1)	1 : 11	88
2		Me	Ph	Ph	-78°C, 1h (1)	1 : 15.6	78
3		Me	Me	OEt	-78°C, 20 min (2.4)	1 : 6[b]	70
4		Me	Me	OEt	-78°C, 2h (2.4)	1 : 5.3[b]	61
5	*Z*	Me	Me	Me	-78°C, 1h (1)	3 : 1	80
6		Me	Ph	Ph	-78°C, 1h (1)	2.7 : 1	75
7		Me	Me	OEt	-78°C, 1h (2.4)	4 : 1	75
8		Me	Me	OEt	-78°C,6h,-40°C,4h(2.4)	11.2 : 1[c]	65
9		Me	Me	OPr^i	-78°C,5h,-40°C,4h(2.4)	11 : 1[c]	68

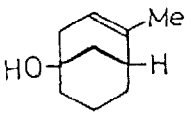
a. The ratios were determined by capillary GC analyses.
b. The formation of the cyclization products in minute amount was discernable by TLC.
c. In addition, a mixture of the cyclization products could be separated by chromatography.

If this is possible, juvabione (**1**) and *epi*-juvabione (**2**) can easily be synthesized from products **4** and **5**. The requisite *Z*- and *E*-allylsilanes were prepared with stereo-purity of over 99% by the method of Kumada.[6] The addition reaction was conducted in CH_2Cl_2 solution with $TiCl_4$ essentially as reported by Hosomi and Sakurai.[7] The stereochemistry of diastereomeric products **4** and **5** was assigned by a chemical correlation to the known alcohols **6** and **7**.[8,9] The results are reproduced in Table 1.

The double bond geometry plays a principal role in the diastereoselection, *E*- and *Z*-crotylsilanes showing *erythro* and *threo*[4,10] selectivities respectively. Better selectivities were generally observed in the reactions with *E*-crotylsilanes. On the other hand, the effect of the silyl substituents was hard to correlate with their electronic or steric features. The best *erythro*-selectivity was obtained using methyldiphenylcrotylsilane(entry 2). The major complicating factor was the dependence of the diastereoselectivity on the temperature and the time in the reaction with *Z*-alkoxycrotylsilanes (entries 4 *vs.* 3 and 8 *vs.* 7), where more than two equivalents of the Lewis acid were necessary for the smooth reaction to occur.[11] We found that the reason for this intricacy was the secondary reaction of the addition products **4** and **5** caused by the excess of Lewis acid and that the *erythro* keto-olefin **5** suffered this side reaction more easily than the *threo* keto-olefin **4**. When an *erythro*-major mixture of the keto-olefin(**4**/**5** = 1:14) was treated with one equivalent of $TiCl_4$, the reaction was completed within 5 minutes even at -78 °C, giving a mixture of two products in an approximate ratio of 1:1, to which the bicyclo[3.3.1]nonane structures **8** and **9** were assigned on the basis of spectroscopic analysis.[12,13] The same treatment of *threo*-major mixture (**4**/**5** = 7.8:1) for 30 minutes resulted in the reaction proceeding nearly half way to yield the mixture of the cyclization products above, and the diastereomer



6 R^1=H;R^2=Me
7 R^1=Me;R^2=H



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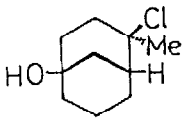

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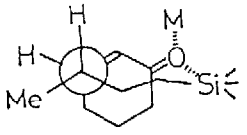

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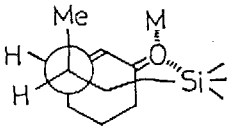

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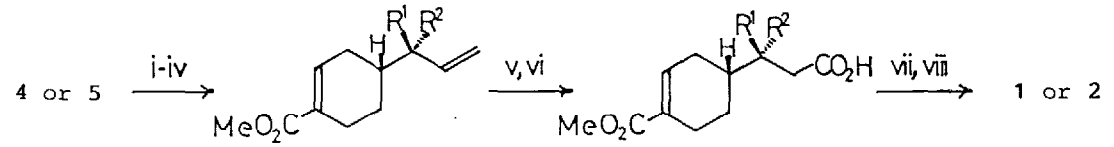
ratio of the remaining starting material had changed to 17:1. Eventually the occurrence of the secondary reaction sanctified the enhancement of the *threo* selectivity in the reaction with *Z*-alkoxycrotylsilanes (entries 8 and 9).[11]

The observed selectivity (high *erythro* for *E*-crotylsilanes and low *threo* for *Z*-crotylsilane) is hard to reconcile with supposition of the relevant transition state. The antiperiplanar disposition as in the open-chain model[15] is untenable. Our present assumption is that synclinal transition states like **10** and **11** might be favored by the O-Si interaction[16] between the silyl and the coordinated carbonyl groups.[17]

Next, we performed the stereoselective syntheses of both (±)-juvabion (**1**) and (±)-*epi*-juvabione (**2**) in a concise manner as shown in Scheme 2, starting from the diastereomerically enriched keto-olefins obtained above(**4**/**5** = 11.2:1 and 1:15.6 respectively). The functional conversion on the cyclohexane ring was carried out by the established procedure[4] to afford dienic esters **12** and **13**, which were selectively hydroborated and oxidized. The obtained acids **14** and **15** could be purified by recrystallization in both cases (m.p. 55.5- 56.5 and 88-90 °C, respectively). The acid chlorides derived from **14** and **15** were transformed to (±)-juvabione (**1**) and (±)-*epi*-juvabione (**2**) by the method of Marchese and his colleagues.[18] In the ^{13}C NMR spectra both synthetic products have been confirmed to exhibit the same minor difference in chemical shifts as reported for natural products.[19]



12 R^1=H;R^2=Me
13 R^1=Me;R^2=H

14 R^1=Me;R^2=H
15 R^1=H;R^2=Me

Scheme 2 Reagents: (i) NaH-$CO(OMe)_2$/THF; (ii) $NaBH_4$/*i*-PrOH; (iii) MsCl-Et_3N/CH_2Cl_2; (iv) MeONa/MeOH; (v) $(C_6H_{11})_2BH$/THF; (vi) CrO_3-H_2SO_4/Et_2O; (vii) $(COCl)_2$/benzene; (viii) Me_2CHCH_2MgBr-$Fe(acac)_2$/THF

Acknowledgements: We thank Prof. S. Isoe for the sample of todomatuic acid and Prof. K. Mori for the copies of ^{1}H NMR spectra of synthetic juvabiones.

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9. The mixtures with different ratios(**4**/**5** = 3.5:1 and 1:7) were converted to those of the known alcohols **6** and **7** by a following sequence of reactions and the ^{1}H NMR chemical shifts of secondary methyl signals were compared with the values reported[8]: (i) LDA/THF; (ii) MeI; (iii) $LiAlH_4/Et_2O$; (iv) $MsCl\text{-}Et_3N/CH_2Cl_2$; (v) O_3/MeOH; (vi) $NaBH_4$; (viii) DBU, Δ.
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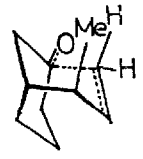
11. This fact is probably due to the attenuation of the Lewis acid strength by the complexation with the alkoxy group, which also moderate the side reactions. Thus the reaction of *Z*-crotylsilane having no alkoxy group in the presence of excess Lewis acid resulted in the deterioration of the products without substantial improvement of the *threo* ratio.
12. **8**: MS(M$^+$)*m*/*z*=152; IR(neat)3700,3550,770 cm^{-1}; ^{1}H NMR(CD_3Cl) δ1.24-1.86(m, 10H),1.61(dt,J=1.9,2.2Hz,3H),2.12(ddq,17.2,5.8,2.2,1H),2.20(ddq,J=17.2, 4.8,2.2,1H),5.37(ddq,J=5.8,4.8,2.2); ^{13}C NMRδ20.0(t),21.6(t),26.6(t),39.0 (d),41.1(t),41.2(t),42.1(t),69.1(s),121.06(d),121.12(s). **9**: MS(M$^+$) *m*/*z*= 188,190; IR(neat) 3620,3430,710 cm^{-1}; ^{1}H NMR δ1.4-2.4(m,14H),1.63(3H,s); ^{13}C NMR δ21.3(t),26.7(t),31.3(q),36.2(t),39.8(t),39.8(t),40.1(t),46.1 (d),69.0(s),75.26(s).
13. The easier cyclization of the *erythro* isomer **5** would be explained as follows. In the 'twin-chair'-like[14] transition state the one derived from the *threo* isomer **4** would be energitically unfavored by the presence of A^{1,3} repulsion and the axial-like disposition of the methyl substituent as depicted in **16**.



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17. These eight-membered cyclic transition states pertain to the one original -ly mentioned by Yamamoto.[15] The difference of the methyl group conformation between **10** and **11** (pseudoequatorial and pseudoaxial respectively) might be reflected in the degree of the diastereoselectivities for the reactions with *E*- and *Z*-crotylsilanes. Suggestively in the preliminary results of the reactions with *Z*- and *E*-tri-*n*-butylcrotylstannanes the same trend in the diastereoselectivity was observed with respect to the double bond geometry but the selectivity was much lower.
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19. J. F. Manville and K. Bock, *Org. Mag. Res.*, **9**, 596(1977). This represents only available spectroscopic method sofar for the discrimination between **1** and **2**. In addition we noticed that they showed delicate but distinct variation in 400 MHz ^{1}H NMR spectra in the signals due to *gem*-dimethyl protons(**1**: δ0.910,0.916; **2**: δ0.910,0.918) and the signal due to methylene protons at C-3(**1**: δ1.751,1.941; **2**: δ1.751,1.900).

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