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STEREOSELECTIVE CYCLIZATION OF (*E*)- AND (*Z*)-5,6-DIMETHYL-8-TRIMETHYLSILYL-6-OCTENALS

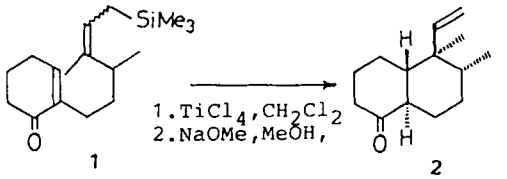
Kazuhiko Asao, Hideo Iio, and Takashi Tokoroyama*
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Summary: The diastereoselectivities in the acid-mediated cyclization of (*E*)- and (*Z*)-5,6-dimethyl-8-trimethylsilyl-6-octenals, both stereoselectively synthesized, were investigated. Excellent preference for the formation of *cis*-dimethylcyclohexanols was realized, specially in the case of the (*Z*)-substrate where they formed exclusively. The selectivity in the hydroxyl group configuration varied in relation with the double bond geometry of the substrates and the acid reagents used.

Recently we have proposed the concept of folding strain control in relation with the highly stereocontrolled cyclization of 2-(6'-trimethylsilyl-3',4'-dimethyl-4'-hexenyl)-2-cyclohexenone (**1**) to decalone derivative **2**[1,2] (Scheme 1). For examination of this sort of stereocontrol in a simpler system and also for utilization of the cyclization product to natural product syntheses,[3] the diastereoselectivities in the cyclization of (*E*)- and (*Z*)-5,6-dimethyl-8-trimethylsilyloctanals, (**3**) and (**4**), were investigated (Scheme 2).

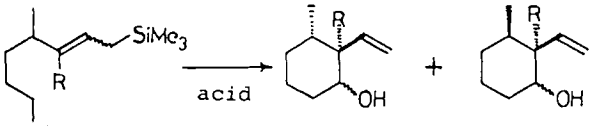
The allylsilane substrate **3** and **4** were synthesized by the silylation[4] of corresponding halides **9** and **11**, which in turn were respectively prepared in stereoselective ways as shown in Scheme 3.[5,7] The cyclization was performed in the presence of various acidic reagents and the product cyclohexanols were obtained generally in high yields. Whereas the *E*-substrate gave all of four

Scheme 1



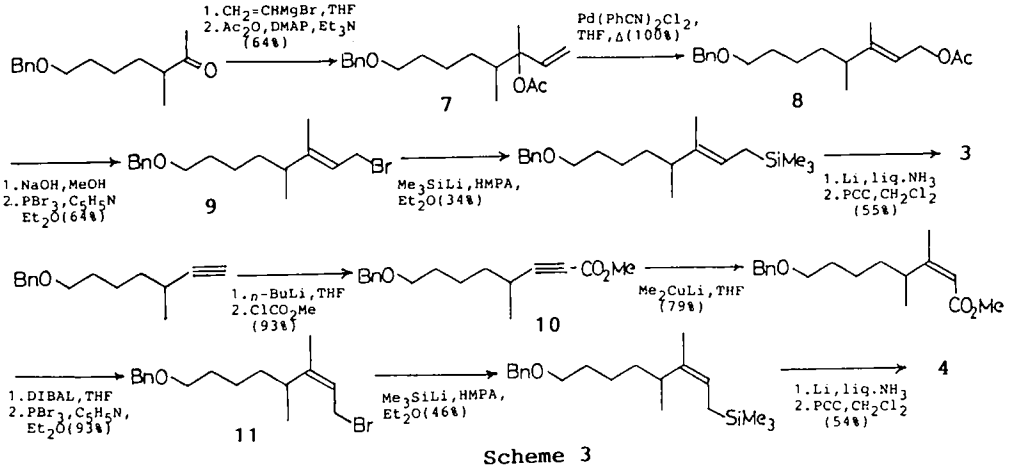
1 2

Scheme 2



3 Δ=*E*; R=Me
4 Δ=*Z*; R=Me
12 Δ=*E*; R=H
13 Δ=*Z*; R=H

5a R=Me; α-OH 6a R=Me; α-OH
5b R=Me; β-OH 6b R=Me; β-OH
14a R=H; α-OH
14b R=H; β-OH



Scheme 3

possible diastereomers, the *Z*-educt afforded only two isomers **5a** and **5b.** The configuration of these products was assigned by the spectral comparison with the authentic specimen.[8] The results are reproduced in Table. The configurational preference of the secondary methyl groups in the products, which is concerned with the diastereoface selection, is *trans* with reference to the vinyl group (*i.e.* cis-dimethyl group), regardless of the double bond geometry of the substrates. The *trans*-selectivity is practically complete in the cyclization of the *Z*-allylsilane **4**, whereas the *E*-educt **3** showed the *trans*-selectivity of 83-91%. As for the hydroxyl group configuration relative to the vinyl group, which has to do with the simple diastereoselection, *trans*-product formed predominantly in the cyclization of *E*-substrate **3.** In the case of the *Z*-substrate **4** this tendency decreased and the formation of *cis*-product became comparable. The dependence of the stereoselectivity on the acid

Table. Diastereoselectivities in the Cyclization of 5,6-Dimethyl-8-trimethylsilyl-6-octanals[a]

entry	substrate	acid reagent	temperature (°C)	time (min)	Product ratio (%)[b] 5a	5b	6a	6b	Yield (%)
1	**3**	CF_3CO_2H	-20	5	73	10	14	3	90
2	**3**	$SnCl_4$	-78	10	83	8	7	2	90
3	**3**	$BF_3 \cdot Et_2O$	-78	10	78	8	6	6	80
4	**4**	CF_3CO_2H	-20	5	56	50	0	0	90
5	**4**	$SnCl_4$	-78	10	61	39	0	0	90
6	**4**	$BF_3 \cdot Et_2O$	-78	10	70	30	0	0	80

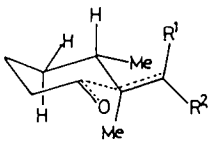
[a]The reaction was conducted by the addition of the acid reagent (0.4 mmol) to a solution of the substrate (0.3 mmol) in CH_2Cl_2 (2 mL) cooled to the specified temperature.
[b]The ratio was estimated from the integral of the methyl singlets in the 400 MHz ^{1}H NMR spectrum.

reagents was not distinctive.[9]

For reference we also investigated the selectivity in the cyclization of corresponding disubstituted allylsilanes **12** and **13**.[10] In the reactions of both *E*- and *Z*-substrates, only two products **14a** and **14b** with *trans* methylvinyl configuration were detected.[14] Interestingly the stereoselection with respect to the hydroxyl group reversed from *E*- to *Z*-substrates. Thus the *E*-allylsilane **12** gave preferentially the cyclohexanol **14a** with *trans*-hydroxyl group (*trans*/*cis* ratio: CF_3CO_2H, >5 : 1; $SnCl_4$, >3 : 1), and in the case of *Z*-allylsilane **13**, the *cis*-product **14b** was predominant (*cis*/*trans* ratio: CF_3CO_2H, >100 : 1, $SnCl_4$, >3 : 1).

The *trans*-preference with the configuration of the sec methyl group, which is the desired sense in the designed natural product syntheses,[3] can be reasonably predicted from the concept of the folding strain control.[2] The transition state folding **16** leading to the *cis*-product would be doubly destabilized by the $A^{1,3}$ repulsion present between R^1 and the sec methyl group, and the additional gauche interaction with the adjacent methylene group in comparison with the folding **15**, which give the *trans*-product. The exertion of more effective $A^{1,3}$ repulsion in the case of *Z*-substrate (R^1 = CH_2Si- instead of H) is in good conmformity with the observed better selectivity.

The explanation of the selectivity observed with respect to the hydroxyl group configuration is more complicated. As for the disposition of the allylsilane group the pararell form like **15** (or **16**) would be more favored than the crossed form[15] from steric reason.[16] Then the selectivity in the disubstituted substrates indicates that the reactions of *E*- and *Z*-substrates, **12** and **13**, prefer *exo* and *endo* orientation of the aldehyde group respectively. This means that the actual donor and acceptor atoms tend to be close to each other in synclinally disposed π-systems and follows the general topological rule summarized by Seebach.[17] The origin for the *syn*-preference would be ascribed to the secondary orbital interaction as assumed recently for the reaction of an allylstannane system.[18] The selectivity in the trisubstituted substrates **3** and **4** can be interpreted as the perturbation of the disubstituted case introduced by the presence of the vinyl methyl group. The *trans*-selectivity in the *E*-substrate and *cis*-selectivity in the *Z*-substrate both decreased, the extent of latter change being remarkable. The explanation could be the destabilization of the transition state **18** due to the location of the vinyl



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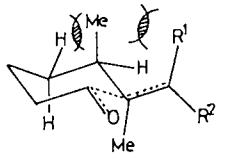

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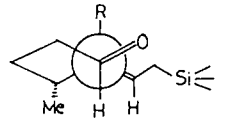

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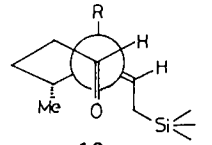

18

methyl group in more crowded outside position.[19]

References and notes

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5. In the synthesis of *E*-halide **9** palladium-catalyzed rearrangement of the allylalcohol **7** was used as a key step, which afforded *E*-stereoisomer **8** exclusively in present case. cf. Y. Tamaru, Y. Yamada, H. Ochiai, E. Nakajo, and Z. Yoshida, *Tetrahedron*, **40**, 1791 (1984). For the preparation of the *Z*-halide the stereoselective addition of cuprate to propiolate **10** was effectively used.[6]
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7. An alternate stereodivergent synthesis of these compounds has also been developed: K. Asao, H. Iio, and T. Tokoroyama, *Synthesis*, submitted.
8. The authentic specimens were prepared as follows. The conjugate addition-alkylation (Me_2CuLi, then CH_2=$CHCH_2Br$) of 2-methyl-2-cyclohexenone furnished a diastereomeric mixture of 2,3-dimethyl-2-allylcyclohexanone, which, after ketalization, was ozonized and then reduced with $NaBH_4$. The obtained mixture of 6-(2-hydroxyethyl)-6,7-dimethyl-1,4-dioxaspiro[4.5]-decane (*cis*/*trans* = 4.5:1 were separated by silica gel chromatography and each product was subjected to a sequence of reactions: (i) *o*-$NO_2C_6H_4SeCl$, *n*-Bu_3P; (ii) 30% H_2O_2, THF, C_5H_5N; (iii) 85% CF_3CO_2H, THF; (iv) L-Selectride, THF. From the *cis*-dimethylalcohol **5a** and **5b** were obtained and from *trans*-dimethyl compound **6a** and **6b** were derived. ^{1}H NMR: **5a**, δ 0.76(d, 3H, J = 6.8 Hz), 0.85(s, 3H), 3.28(dd, 1H, J = 4.2,11.0 Hz), 5.09(dd, 1H, J = 1.2, 17.6 Hz), 5.21(dd, 1H, J = 1.2,11.0 Hz), 5.59(dd, 1H, J = 11.0, 17.6 Hz); **5b**, δ 0.78(d, 3H, J = 6.8 Hz), 0.91(3H, s), 3.41(t, 1H, J = 2.9 Hz), 5.07(dd, 1H, J = 1.2,17.9 Hz), 5.21(dd, 1H, J = 1.2,11.1 Hz), 5.84(dd, 1H, J = 11.1,17.9 Hz); **6a**, δ 0.82(d, 3H, J = 6 Hz), 1.13(3H, s), 4.96-6.13(3H, ABX); **6b**, δ 0.84(d, 3H, J = 6 Hz), 1.09(s, 3H), 4.96-6.13(3H, ABX).
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10. The compounds **12** and **13** were synthesized by the coupling of the corresponding vinyl halides with trimethylsilylmethylmagnesium chloride according to Kumada-Tamao procedure.[11] In turn the *E*-vinyl bromide was prepared through bromination of (*Z*)-7-benzyloxy-3-methyl-1-trimethylsilyl-1-heptene and subsequent base treatment,[12] and the *Z*-vinyl iodide was obtained from 7-benzyloxy-3-methyl-1-heptynyl iodide by diimine reduction.[13]
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14. The reaction was somewhat less clean in comparison with the trisubstituted case, giving the cyclization product in 50-60% yield. The diastereomer ratios were estimated from the integral of the signals due to the proton attached to the hydroxyl group bearing carbon atom in 90 MHz NMR spectra.
15. The notation indicates the relative disposition of the donor (allylsilane) group to the C1-C2 bond of the aldehyde group.
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