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Alternation of Stereocontrol Mode in the Cyclization of 2-(3',4'-Dimethyl-6'-trimethylsilyl-4'-hexenyl)-2-cyclohexenones by the Auxiliary Controlling Substituents at 1'- and 2'-Positions of the Side Chain

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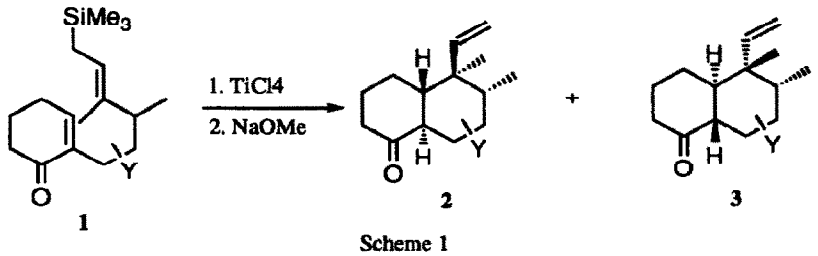
Abstract: With the aim to alter the stereochemical mode in the cyclization of the title compound the diastereoselectivities in that of the substrates with an oxy-substituent at 1' and 2' positions of the side chain were investigated. In the cyclization of the substrate with the 2'-oxy-substituent its controlling effect was not enough to reverse the diastereoselectivity. On the other hand the cyclization of the substrates with the 1'-oxy-substituent proceeded under its ensuing elimination to afford the octalone derivatives with a variety of stereochemical outcomes. Through the choice with respects to kinds and stereochemistry of the oxy-substituent, and the Lewis acids, the respective stereoselective formations of the three diastereomers out of four including the octalone derivative with 8,9-*trans*-dimethyl configuration were achieved.

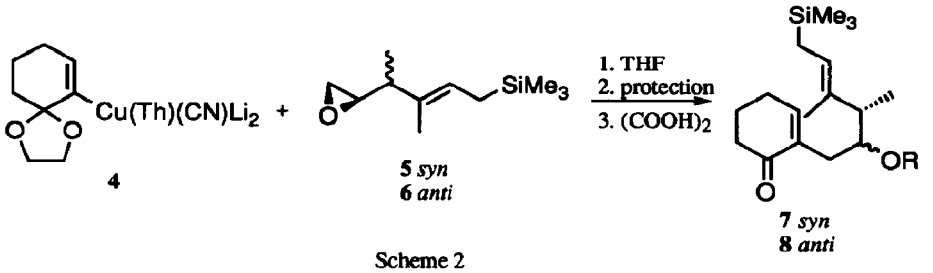
Previously we reported the cyclization of title compound **1** (Y = H) proceeded under complete double diastereocontrols (simple diastereo and diastereoface selections) to afford the diastereomer **2** (Y = H) exclusively after equilibration with sodium methoxide.[1] By the application of this reaction a one-pot construction of the 8,9-*cis*-dimethyl-*cis*-fused clerodane skeleton was acomplished.[2] Subsequently we observed the stereocontrol mode in the cyclization was altered by the presence of an 2'-*anti*-methyl group in the substrate **1** to give pre-dominantly a 8,9-*trans*-dimethyl derivative (**3**, Y = 7α-Me).[3] This result indicates that, by the use of 2'- or possibly 1'-substituent Y as a removable controlling group, the stereoselective construction of 8,9-*trans*-dimethylclerodane skeleton, a naturally occurring stereochemical variant,[4] could be realized. In this letter we delineate the result of our investigation directed toward such an end using oxy-substituent as the controlling group.



1 **2** **3**

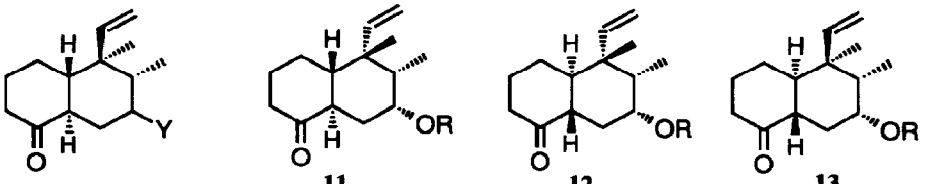
Scheme 1

We investigated first the cyclization reaction of diastereomeric 2'-oxy-substituted allylsilane substrates **7** and **8**, which were synthesized by coupling of 2-lithio-1-ethylenedioxy-2-cyclohexene as a higher order cuprate **4** with *syn*- and *anti*-(*E*)-1,2-epoxy-3,4-dimethyl-6-trimethylsilyl-4-hexenes **5** and **6**[5], respectively, albeit both in low yields (~ 20%).[6] Cyclization of the *syn*-acetoxy substrate (**7**, R = Ac) gave, after equilibration, 8,9-*cis*-dimethyl product **9**[7] exclusively as expected. In contrast the cyclization of the *anti*-substrates **8a** (R = Ac) and **8b** (TBDMS) gave four diastereomers **10**, **11**, **12**, and **13**[8] in ratios of 7.7: 1: 2.4: 0 and 4: 1: 2: 2 respectively. Although the formation of desired 8,9-*trans*-dimethyl compound **12** was confirmed in these cyclizations, the selectivity remained too low to be synthetically useful. The result indicated that the strain ener-



Scheme 2

gy difference of diastereomeric transition states caused by the oxy-substituents with relatively small A-values was not enough to make the reaction selective.

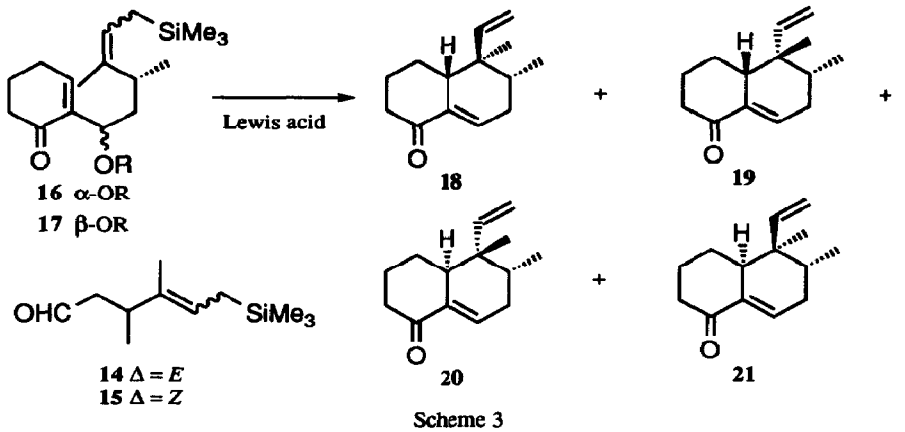


9 Y = β-OAc
10a Y = α-OAc
10b Y = α-OTBDMS

11 **12** **13**

Subsequently our attention was moved to the control of the cyclization mode of **1** by the introduction of 1'-oxy-substituent from the expectation that it might affect the energy difference between the diastereomeric transition states effectively through additional perturbation caused by the *peri*-interaction with the carbonyl group of the cyclohexene ring, which could act attractive (chelation) or repulsive (steric and dipolar). The pair (*syn* and *anti*) of diasteromeric cyclization substrates **16** and **17** for *(E)* and *(Z)*-series were synthesized by the reaction of corresponding allylsilane aldehydes **14** and **15**, each prepared stereoselectively[9] with 2-lithio-1-ethylenedioxy-2-cyclohexene, and subsequent deketalization and chromatographic separation on silica gel column. The stereochemistry for the *E* pair was detrermined through the X-ray crystallographic analysis of the *p*-bromobenzoate derived from the *anti* diastereomer *(E)*-**17** and that of *(Z)*-isomers was assigned from the ^{1}H NMR comparison with reference to the difference observed between the *(E)*-counterparts. The diastereomeric pairs **16** and **17** were converted respectively to *t*-butyldimethylsilyloxy, methoxymethoxy, methoxy, and acetoxy derivatives, which were subjected to the cyclization reaction with $TiCl_4$ or BF_3·OEt_2. Generally there obtained a mixture of all of the four possible diastereomeric Δ^8-1-octalone derivatives **18-21**, formed by the cyclization and concomitant elimination of the oxy-substituents. Their configurations were assigned on the basis of ^{1}H NMR analysis, having been confirmed for **20** and **21** by single crystal X-ray analysis of the derivatives[11] and for **18** by the chemical conversion *via* the Birch reduction to the octalone derivative previously obtained.[1] The results are summarized in the Table 1.

Although the diastereomeric outcome in the cyclized products is rather complicated and seems not to be correlated simply with the substrate configuration (*syn* or *anti*), kinds of the oxy-substituent or the Lewis acid ($TiCl_4$ or BF_3·OEt_2), the several distinct propensities were noted and some comments are to be made with relation to the cause of the selectivity. (1) The definite dependance of the stereochemical preference to the oxy-substituents indicates its elimination occurs after the cyclization at least for the most part. (2) Generally dominant bias is for the formation of the diastereomer **18** under normal orientation and folding strain stereo-controls.[1,3,12] Preference for the formation of **18** is *syn* < *anti*. This fact indicates that a clinal rather than a



Scheme 3

synperiplanar transition state is favored even when the bidentate $TiCl_4$ is used. An exception is the case of the MeO-substrate, *(E)* where $TiCl_4$ chelates effectively and preference for the formation of **18** was the highest for the reaction, *syn*/$TiCl_4$. (3) In the *syn*-substrates the cyclization more tends to produce the octalone **20** or **21**. Specially in the *(E)*-substrate the preferential formation of **20** is noted in the cases of *syn*-TBDMS/$TiCl_4$ and *anti*-TBDMS/ BF_3-Et_2O. In the former case the severe *peri* repulsive interaction would compelled the reaction to pass through the [b-n-r]-TS. In the latter case the driving force for adoption of the [b-n-r]-TS might be some energetically favorable interaction existing between the carbonyl oxygen and the silicon atoms. Contrastingly in

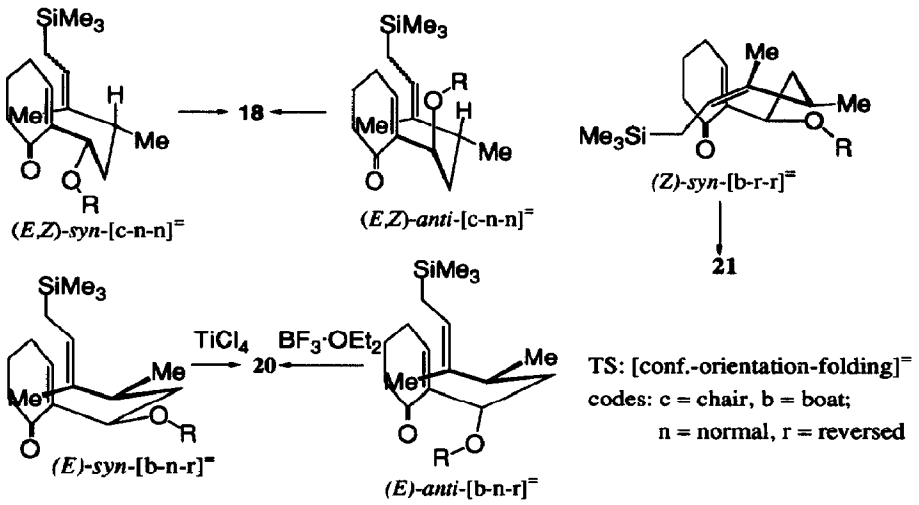
Table 1. Diastereoselectivities in the cyclization of diastereomeric 1'-oxy-substituted 2-(3',4'-dimethyl-6'-trimethylsilyl-4'-hexenyl)-2-cyclohexenones

	substrate			formation ratio[a, b, c]									
				from *(E)*-substrate					from (Z)-substrate				
	R	config.	Lewis acid	**18** : **19** : **20** : **21** (yield, %)					**18** : **19** : **20** : **21** (yield, %)				
16a	TBDMS	*syn*	$TiCl_4$	13	0	74	13	(77)	10	0	3	**87**	(60)
16a	TBDMS	*syn*	BF_3-OEt_2	**68**	12	9	11	(56)	**84**	3	0	13	(57)
16b	MOM	*syn*	$TiCl_4$	24	0	20	**56**	(50)	19	0	0	**81**	(70)
16b	MOM	*syn*	BF_3-OEt_2	**86**	14	0	0	(78)	**84**	5	0	11	(22)
16c	Ac	*syn*	$TiCl_4$	10	0	13	**77**	(96)	7	0	0	**93**	(99)
16c	Ac	*syn*	BF_3-OEt_2	20	0	38	42	(71)	16	0	6	**78**	(58)
16d	Me	*syn*	$TiCl_4$	**97**	0	0	3	(50)	**92**	0	0	8	(92)
16d	Me	*syn*	BF_3-OEt_2	**73**	15	6	6	(71)	**79**	7	0	14	(73)
16a	TBDMS	*anti*	$TiCl_4$	**83**	10	7	10	(77)	**95**	0	2	3	(84)
17a	TBDMS	*anti*	BF_3-OEt_2	12	5	**71**	12	(66)	16	1	25	**58**	(42)
17b	MOM	*anti*	$TiCl_4$	**79**	15	6	0	(80)	**97**	0	0	3	(77)
17b	MOM	*anti*	BF_3-OEt_2	**80**	12	8	0	(72)	**51**	0	10	39	(28)
17c	Ac	*anti*	$TiCl_4$	**95**	3	0	2	(88)	**96**	0	0	4	(94)
17c	Ac	*anti*	BF_3-OEt_2	**81**	19	0	0	(86)	**91**	6	0	3	(77)
17d	Me	*anti*	$TiCl_4$	26	21	31	22	(81)	**58**	0	0	42	(52)
17d	Me	*anti*	BF_3-OEt_2	**70**	15	15	0	(70)	**64**	9	4	23	(73)

a The reactions with $TiCl_4$ and BF_3-OEt_2 were conducted in CH_2Cl_2 solution respectively at -78 °C and at ambient temperature for 30 min.

b The formation ratios were determined from the integral of terminal methylene signals in ^1H NMR spectra.

c The selectivities over 50% are listed as bold letters.



Scheme 4

the *(Z)-syn*-substrate an explicit trend for formation of the octalone **21.** By adoption of the reversed orientation the folding of the chain leading to TS could escape from the severe double gauche interaction exerted to the allylsilane methylene group and $A^{(1,3)}$ strain. Thus in the cyclization of the 1'-oxy-substituted 2-(3',4'-dimethyl-6'-trimethylsilyl-4'-hexenyl)-2-cyclohexenones the stereoselective preparation of three diastereomeric octalones was proved to be virtually feasible through the oxy group modification and, the choice of substrate stereochemistry and the Lewis acid. The result would be quite intriguing in view of stereoselective methodology[13] and, moreover, the products **18** and **20** could be the useful intermediates respectively for the syntheses of 8,9-*cis*- and *trans*-clerodane diterpenoids. Studies toward this direction is now in progress.

References and Notes

1. Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067-5070.
2. Tokoroyama, T.; Tsukamoto, M.; Asada, A.; Iio, H. *Tetrahedron Lett.* **1987**, *28*, 6645-6648.
3. Tokoroyama, T.; Okada, K.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1572-1573.
4. Meritt, A.T.; Ley, S.V. *Nat. Prod. Rep.* **1992**, *9*, 243-287.
5. Both compounds were synthesized from *anti*-3,4-dimethyl-6-trimethylsilyl-4-hexen-1,2-diol, prepared *via* the Ireland rearrangement of 3-methyl-1-trimethylsilyl-3-penten-2-yl benzyloxyacetate, by stereodivergent epoxy formation.
6. Failure in the reaction of the corresponding usual cuprate with an epoxide was reported: Majetich, G.; Leigh, A.J.; Condon, S. *Tetrahedron Lett.* **1991**, *32*, 605-608.
7. Clerodane numbering is used.
8. The configurations were assigned with the aid of 400 MHz NMR analysis.
9. The *(E)*-aldehyde **14** was synthesized by $LiAlH_4$ reduction and subsequent PCC oxidation of 3,4-dimethyl-6-trimethylsilyl-4-hexenoic acid obtainable stereoselectively through the Ireland rearrangement of *(E)*-3,4-dimethyl-1-trimethylsilyl-3-penten-2-yl acetate. The *(Z)*-aldehyde **15** was prepared by the application of our stereoselective method for the synthesis of trisubstituted allylsilanes,[10] starting from ethyl 6-benzyloxy-3-oxohexanoate.
10. Asao, T; Iio, H; Tokoroyama, T. *Synthesis* **1990**, 383-386.
11. The product **20** was converted to (1R*,2R*, 4aR*, 5S*, 8aS*)-1,2,4a,5,6,7,8,8a-octahydro-5-*p*-bromobenzoyloxy-1,2,4a-trimethyl-1-vinylnaphthalene and **21** was transformed to the *p*-bromophenylurethane of corresponding β-alcohol.
12. These controls corresond to the simple diastereo and the diastereoface selections respectively.
13. We propose to call this type of the effect by the name of puppet stereocontrol in the sense that the 1'-oxy-substituent would take a role of something like the manipulating devices in a puppet.

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