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Extracyclic Stereocontrol in Addition Reaction of Crotylsilanes with 2-Substituted 2-Cyclopentenones. Stereodivergent Synthesis of (+)-Neonepetalactone and (+)-Isoneoneptalactone[1)]

Li-Rui PAN and Takashi TOKOROYAMA*
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558

The addition reaction of *E*- and *Z*-crotylsilanes with 2-substituted 2-cyclopentenones showed the preference of *erythro* and *threo* products respectively. The refinement of the selectivity was investigated and the result was utilized for efficient syntheses of the title natural products.

Extracyclic stereocontrol[2,3)] in cyclopentane ring is a problem of current interest specially in connection with the stereoselective construction of steroid side chain.[4)] Precedently we reported a stereospecific addition of *E*- and *Z*-crotylsilanes to 2-cyclohexenone and utilization of the adducts for the stereodivergent synthesis of juvabione and *epi*-juvabione.[5)] We describes here the extension of this extracyclic methodology to the stereoselective synthesis of cyclopentane derivatives.

E- and *Z*-crotylsilanes (**2** and **3**), prepared stereoselectively,[6)] were allowed to react with 2-substituted 2-cyclopentenones (**1**) in dichloromethane solution in the presence of a Lewis acid, usually titanium tetrachloride at -78 °C for 1-4 hours. The diastereomeric ratio[7,8)] of *erythro* and *threo* products (**4** and **5**) are reproduced in the Table 1. As a whole the *erythro*- and *threo*-selectivities[9)] were secured for the reactions of *E*- and *Z*-crotylsilanes (**2** and **3**) respectively in common with the tendency observed in the addition to 2-cyclohexenone.[5)] In comparison with the latter case the selectivities observed in the reaction with 2-cyclopentenone (**1a**) was lowered for *erythro* (entry 1, the corresponding ratio with 2-cyclohexenone was 93:7) and of similar degree for *threo* (entry 2). Substitution at the 2-position tended to increase *threo* selectivity (entries 4-6).

Focussing on the reaction with 2-ethoxycarbonyl-2-cyclopentenone we investigated to improve the diastereo-selectivity. The use of boron trifluoride etherate as the Lewis acid increased somewhat the *erythro*-selectivity (entry 7 *vs.* 9). Modification of the silyl substituents in the *E*-crotylsilane from methyl to phenyl group enhanced the *erythro*-selectivity

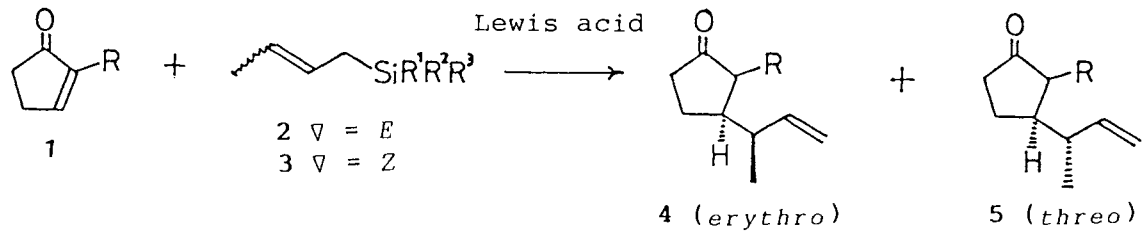


Table 1. Diastereoselectivity in the addition reaction of *E*- and *Z*-crotylsilanes (**2** and **3**) to 2-substituted 2-cyclopentenones (**1**)

Entry	Cyclopentenone	R	Crotylsilane olefin geometry	substituent R^1	R^2	R^3	Lewis acid	Diastereomer ratio (*erythro*/*threo*)
1	**1a**	H	**2c** *E*	Ph	Ph	Me	$TiCl_4$	84 : 16
2	**1a**	H	**3a** *Z*	Me	Me	Me	$TiCl_4$	33 : 67
3	**1b**	Me	**2a** *E*	Me	Me	Me	$TiCl_4$	84 : 16
4	**1b**	Me	**3a** *Z*	Me	Me	Me	$TiCl_4$	8 : 92
5	**1c**	SPh	**3a** *Z*	Me	Me	Me	$TiCl_4$	10 : 90
6	**1d**	CN	**3a** *Z*	Me	Me	Me	$TiCl_4$	20 : 80
7	**1e**	CO_2Et	**2a** *E*	Me	Me	Me	$TiCl_4$	79 : 21
8	**1e**	CO_2Et	**2a** *E*	Me	Me	Me	$TiCl_4$[a]	86 : 14
9	**1e**	CO_2Et	**2a** *E*	Me	Me	Me	$BF_3 \cdot Et_2O$	86 : 14
10	**1e**	CO_2Et	**2a** *E*	Me	Me	Me	$BF_3 \cdot Et_2O$[a]	69 : 31
11	**1e**	CO_2Et	**3a** *E*	Ph	Me	Me	$BF_3 \cdot Et_2O$	87 : 13
12	**1e**	CO_2Et	**3a** *E*	Ph	Me	Me	$TiCl_4$[a]	91 : 9
13	**1e**	CO_2Et	**3a** *E*	Ph	Ph	Me	$TiCl_4$	81 : 19
14	**1e**	CO_2Et	**3a** *E*	Ph	Ph	Me	$TiCl_4$[a]	93 : 7
15	**1e**	CO_2Et	**3a** *Z*	Me	Me	Me	$TiCl_4$	25 : 75
16	**1e**	CO_2Et	**3a** *Z*	Me	Me	Me	$TiCl_4$[a]	30 : 70
17	**1e**	CO_2Et	**3a** *Z*	Me	Me	Me	$BF_3 \cdot Et_2O$	34 : 66
18	**1e**	CO_2Et	**3a** *Z*	Me	Me	Me	$BF_3 \cdot Et_2O$[a]	33 : 67
19	**1e**	CO_2Et	**3a** *Z*	Me	Me	Me	CF_3CO_2H	18 : 82
20	**1e**	CO_2Et	**3c** *Z*	Ph	Ph	Me	$TiCl_4$	28 : 72

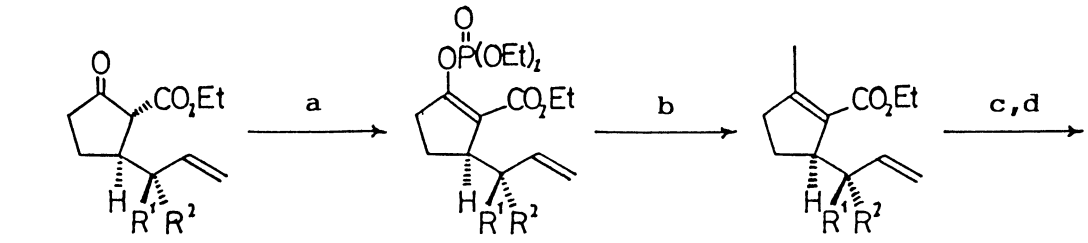
a) HMPA (2.8 equiv.) was added.

only modestly in contrast with the reaction of 2-cyclohexenone (entry 13 *vs.* 7 and 11 *vs.* 9).[5] A considerable improvement was achieved by the addition of hexamethylphosphortriamide (HMPA) in the reaction using titanium tetrachloride as the Lewis acid (entries 8 *vs.* 7 and 14 *vs.* 13) and thus the *erythro* adduct **4** could be obtained with a preference up to 93:7. Interestingly in the reaction with boron trifluoride etherate the use of the addend rather lowered the selectivity (entries 10 *vs.* 9), reflecting the difference in its chelating behavior from that of the foregoing Lewis acid. For enhancement of the *threo*-selectivity neither modification of the silyl substituent nor use of the addend was effective. The reaction in the presence of trifluoroacetic acid gave the best result in which a *threo* selectivity of 82:18 was obtained.

With the demonstration of the feasibility in the stereodivergent preparation of the *erythro* and *threo* products **4e** and **5e**, we undertook the

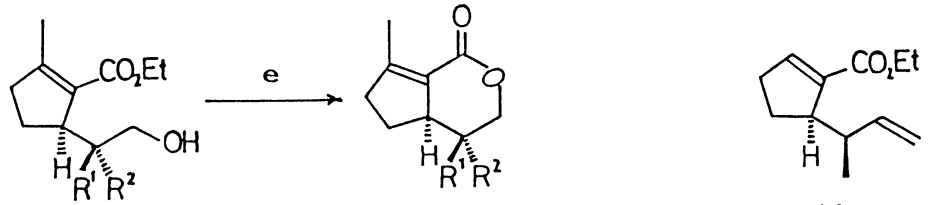
syntheses of neonepetalactone (**9a**) and isoneonepetalactone (**9b**), the constituents cat- and lace wing-attracting plant *Actinidia polygama* Miq.,[10,11] of which stereochemistry has been established.[10] The *erythro*-major adduct (*erythro*/*threo* = 93:7) was first converted to a enol phosphate **6a**. Treatment of **6a** with dimethylcopperlithium gave a 2:1 mixture of the methylated product **7a** and the deoxygenated product **10** in 64% yield. However the application of Ohshima-Nozaki procedure[12] resulted in clean formation of the desired product **7a** in 91% yield which was obtained also stereochemically pure after silica gel chromatography. Oxidative cleavage of the terminal methylene group was performed by Lemiex-Johnson condition rather than by ozonolysis and, after reduction of the so-formed aldehyde group, a hydroxy-ester **8a** was produced. Upon acid treatment the compound **8a** afforded a lactonic product. In the ^{1}H NMR it exhibited the signals due to protons of the hydroxymethylene group at δ 4.18 and 4.34 as the AB pattern of a ABX system (J_{AB} = 11.4 Hz, J_{AX} = 2.6 Hz and J_{BX} = 3.0 Hz), which were in conformity with those of neonepetalactone **9a**.[10,13] When the *threo*-major adducts mixture (*threo*/*erythro* = 90:10)[14] was subjected to the same sequence of the reactions described above, isoneonepetalactone **9b** was obtained. It showed in the ^{1}H NMR spectrum the hydroxymethylene signals at δ 3.81 and 4.20 both as doublets of doublet (J_{AB} = 11.4 Hz, J_{AX} = 11.4 Hz, and J_{BX} = 4.8 Hz) which corroborated the assignment.[3,11,15]

Thus a stereodivergent synthesis of neonepetalactone and isoneonepetalactone has been achieved in a very concise way using our extracyclic



4e R^1 = Me, R^2 = H
5e R^1 = H, R^2 = Me

6 **7**



8 **9** **10**

6-9 **a** R^1 = Me, R^2 = H
b R^1 = H, R^2 = Me

Reagents: a) NaH, $ClPO(OEt)_2$, Et_2O; b) Me_3Al, $PdCl_2(PPh_3)_2$, DIBAL, $ClCH_2CH_2Cl$; c) OsO_4, $NaIO_4$, THF, H_2O; d) $NaBH_4$, MeOH; e) TsOH, C_6H_6

stereocontrol methodology. This method would be useful for the syntheses of the other natural products with extracyclic stereo center and the studies in this line are now in progress in our laboratory.[16]

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7) The assignment of the product configuration has been confirmed by the stereodivergent synthesis of the natural products described below.
8) The ratios were determined by combination of ^{1}H and ^{13}C NMR spectroscopy and capillary GC analyses.
9) The notation based on Noyori's proposal: R. Noyori, I. Nishida, and J. Sakata, *J. Am. Chem. Soc.*, **103**, 2106(1981).
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12) K. Takai, M. Sato, K. Ohshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **57**, 108(1984).
13) ^{1}H NMR($CDCl_3$, 90 MHz): δ 0.95(3H, d, 7.2 Hz), 1.20-2.13(3H, m), 2.20 (3H, t, J=1 Hz), 2.26-2.53(2H, m), 3.13(1H, m), 4.12, 4.32(each 1H, dd, AB part of an ABX system, J_{AX} = 2.6 Hz, J_{BX} = 3.0 Hz, J_{AB} = 11 Hz).
14) The material partially enriched during silica gel chromatography.
15) ^{1}H NMR($CDCl_3$, 90 MHz): δ 0.94 (3H, d, 6.6 Hz), 1.20-2.15(3H, m), 2.20 3H, t, J=1 Hz), 2.27-2.75(3H, m), 3.83, 4.22(each 1H, AB part of an ABX system J_{AX} = 11.3 Hz, J_{BX} = 5 Hz, J_{AB} = 11.3 Hz).
16) It has been shown that the addition reaction described can be performed in asymmetric manner using the cyclopentenone substrate with chiral auxiliaries in the carboxyl group and therefore the asymmetric syntheses of neonepetalactones are now feasible in principle. The asymmetric synthesis of cholesterol C/D ring are under investigation: L.-R. Pan and T. Tokoroyama, 59th. National Meeting of the Chemical Society of Japan, April 1990, No. 4C6-30.

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