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TOTAL INVERSION OF *CIS*-C5 MAXACALCITOL INTO ITS *TRANS*-C5 ISOMER VIA THE SULFORENE INTERMEDIATE

Tsuyoshi Yamauchi,*[a,b] Koji Suzuki,[a] Hitoshi Shimizu,[a] and Masahiro Kato[a]

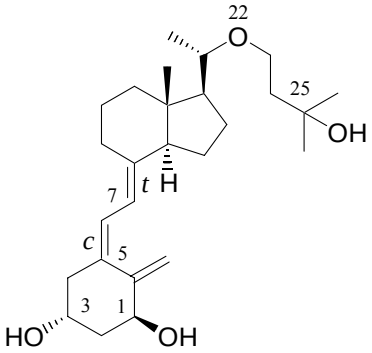
Synthetic Technology Research Department, Chugai Pharmaceutical Co., Ltd., 5-5-1 Ukima, Kita-Ku, Tokyo 115-8543, Japan[a] and Pre-Clinical Research Department, Chugai Pharmaceutical Co., Ltd., 1-135 Komakado, Gotemba, Shizuoka 412-8513, Japan[b]

Abstract – Total inversion of the *cis*-C5 configuration of Maxacalcitol, the unnatural 22-oxa-vitamin D_3 analogue used for the treatment of secondary hyperparathyroidism and psoriasis, into the *trans*-C5 isomer has been accomplished stereoselectively via a formation of the sulforene intermediate for biological evaluation.

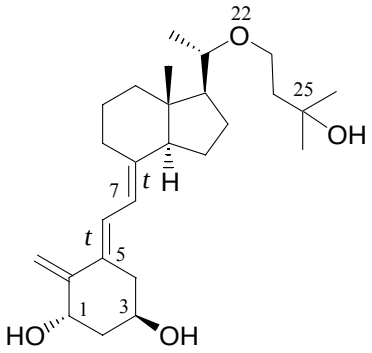
Naturally occurring vitamin D derivatives carry a common conjugated triene system with *cis*-C5 configuration in their molecules.[1] It has been well recognized that their *cis*-C5 configuration may be partially isomerized spontaneously and forcedly completely into the *trans*-C5 configuration.[1,2,3] Maxacalcitol (**1**) is the non-natural vitamin D_3 derivative having a 1α,25-dihydroxyvitamin D_3 framework in which C22-methylene functionality is replaced by an oxygen atom and presently used for the treatment of secondary hyperparathyroidism and psoriasis.[4,5] Because we have so far observed a spontaneous generation of a trace of the *trans*-C5 isomer (**2)** during the industrial preparation of maxacalcitol (**1**), we decided to obtain a substantial amount of the *trans*-C5 isomer by isomerization of the *cis*-C5 precursor (**1**) for its biological evaluation. We report here an efficient method allowing complete isomerization of *cis*-C5 maxacalcitol (**1**) into *trans*-C5 isomer (**2)** (Figure1).

Since the so far observed isomerization has been assumed to be due to light, we first exposed Maxacalcitol (**1**) to sunlight in acetone with expectation of the photosensitizing effect of the ketonic solvent. On exposure to sunlight in acetone in a Pyrex flask under argon at ambient temperature, the expected isomerization did really take place, but decomposed the product at once, to give only 2% yield of the *trans*-C5 isomer (**2**) after 4 h. We, then, examined the isomerization of **1** under the forcing conditions by employing the conditions established for the isomerization of natural vitamin D_2 and D_3

derivatives into the corresponding *trans*-C5 isomers.[2,3,6] Thus, Maxacalcitol (**1**) was stirred with an excess of sulfur dioxide at –15 ºC to initiate the cycloaddition to give sulforene adduct. As expected, the reaction took place facilely within 1 h to form the adduct (**3**) as a mixture of two diastereomers as a solid after evaporation of excess sulfur dioxide. Each of the α-adduct (**3a**) or the ß-adduct (**3b**) could not be clearly determined as the mixture could not be separable even by preparative HPLC. But it was deduced to consist of seven parts of one and three parts of another one by ^{1}H NMR analysis and HPLC analysis.



Maxacalcitol **(1)**

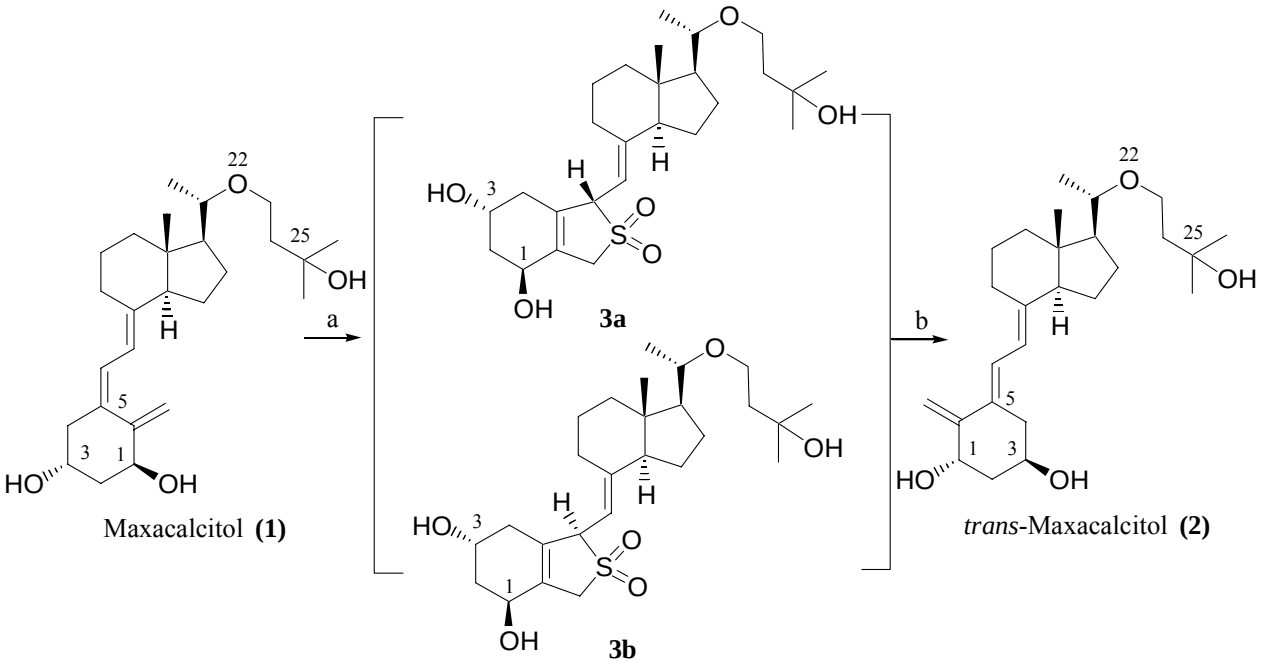


trans-Maxacalcitol **(2)**

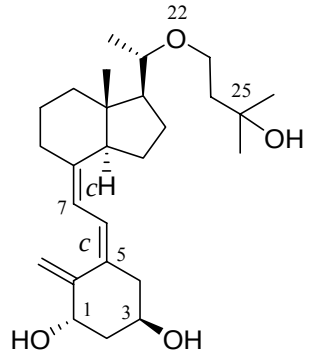
Figure 1

On the basis of the results so far observed in the thermolysis of the sulforenes generated from natural vitamin D derivatives,[6] the adduct mixture (**3**) was refluxed in ethanol in the presence of 6 equiv. of sodium hydrogen carbonate. Cheletropic extrusion of sulfur dioxide took place readily to transform the adduct mixture (**3**) completely into the *trans*-C5 isomer (**2**) of Maxacalcitol (**1**) within 4 h. Overall yield of the *trans*-C5 isomer (**2**) from the *cis*-C5 precursor (**1**) was 70%. As reported in the natural vitamin D derivatives, a considerable decomposition occurred to give none of the *trans*-C5 isomer (**2**) without recovery of the starting material provided that the base was absent. This was apparently due to the acid by-products formed from the sulfur dioxide extruded by the cheletropic reaction. It is also interesting to note that the adduct was inert at all when ethanol was replaced by aprotic 1,3-dimethylimidazoline-2,4-dione (DMI) even at a higher temperature at 120 ºC whether the base was present or not (Scheme 1).

The structure of the *trans*-C5 isomer (**2**) was determined unambiguously by NMR analysis which clearly eliminated two other possible isomers having either the *cis*-C5:*cis*-C7 structure (**4)** or the *trans*-C5:*cis*-C7 structure (**5**) (Figure 2).

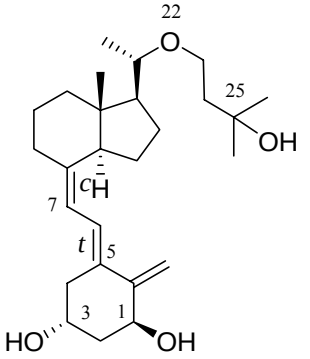


Scheme 1 *Reagents and conditions*: a) *liq.*SO_2, reflux. b) $NaHCO_3$, EtOH, reflux.



cis-C5:cis-C7 structure **(4)**

(*cis-C7 isomer*)



trans-C5:cis-C7 structure **(5)**

(*trans-C5:cis-C7 isomer*)

Figure 2

Although it was unable to distinguish **2** from **4** and **5** by the proton-carbon cross peak experiment as chemical shifts of H4α- and H9β-centers were overlapped when the spectra were measured in $CDCl_3$, fortunately, however, the measurement in DMSO-d_6 solution afforded us clear-cut spectra to make precise analysis possible. After performing four methods (CH-COSY, CH-TOCSY, COLOC, HH-COSY), all the signals could be assigned unambiguously to support the *trans*-C5 structure (**2**) (Table 1). In particular, the NOESY(mixing time 600 ms) experiments revealed the relationships between C6-proton and both one of C19- protons and one of C9-protons as well as the relationship between C7-proton and both of C4 and C15 protons indicating the *trans*-C5 structure (**2**) and eliminating the alternative structures (**4**) and (**5**), unambiguously (Figure 3).

Table 1 ^{13}C and ^{1}H NMR chemical shifts of Maxacalcitol and *trans*-Maxacalcitol in DMSO-*d6*

No.	Maxacalcitol		*trans*-Maxacalcitol	
	Carbon	Proton	Carbon	Proton
1	68.4	4.15～4.25(m)	68.4	4.27(d,t,4.3Hz,5.3Hz)/4.77(OH,d,4.3Hz)
2	43.0	1.50～1.70(β,m)/1.70～1.85(α,m)	42.2	1.72,1.72(d,d,5.3Hz,5.3Hz)
3	65.0	3.98(bs)	64.2	3.85～4.05(m)/4.63(OH,d,5.0Hz)
4	44.8	2.12～2.20(β,m)/2.30～2.40(α,m)	36.3	2.20～2.28(β,m)/2.42～2.50(α,m)
5	135.9	-	135.7	-
6	122.4	6.19(d,11.2Hz)	120.8	6.38(d,11.6Hz)
7	117.7	5.99(d,11.2Hz)	116.4	5.82(d,11.6Hz)
8	139.7	-	142.3	-
9	28.2	1.50～1.70(α,m)/2.79(β,m)	28.3	1.58～1.75(α,m)/2.75～2.85(β,m)
10	149.4	-	153.3	-
11	22.8	1.40～1.50(β,m)/1.50～1.70(α,m)	22.8	1.35～1.55(β,m)/1.55～1.75(α,m)
12	38.8	1.20～1.30(α,m)/1.75～1.85(β,m)	38.9	1.20～1.35(α,m)/1.80～1.90(β,m)
13	44.1	-	44.2	-
14	55.4	1.90～2.00(m)	55.6	2.02(d,d,7.3Hz)
15	21.7	1.40～1.60(m,m)	21.7	1.50～1.65(m,m)
16	24.7	1.40～1.60(β,m)/1.85～2.00(α,m)	24.8	1.40～1.65(β,m)/1.75～1.95(α,m)
17	56.7	1.40～1.50(m)	56.8	1.35～1.65(m)
18	12.2	0.49(s)	12.5	0.50(s)
19	109.8	5.23(Z,s)/4.76(E,s)	107.3	4.87(Z,bs)/4.94(E,bs)
20	76.6	3.17～3.23(m)	76.7	3.17～3.25(m)
21	19.0	1.09(d,5.6Hz)	19.1	1.10(d,6.9Hz)
22	-	-	-	-
23	64.2	3.23～3.33(m)/3.55～3.65(m)	64.3	3.27～3.31(m)/3.56～3.66(m)
24	43.1	1.57～1.67(m,m)	43.2	1.45～1.65(m,m)
25	68.1	-	68.2	4.14(OH)
26	29.5	1.08(s)	29.6	1.09(s)
27	29.6	1.08(s)	29.7	1.09(s)

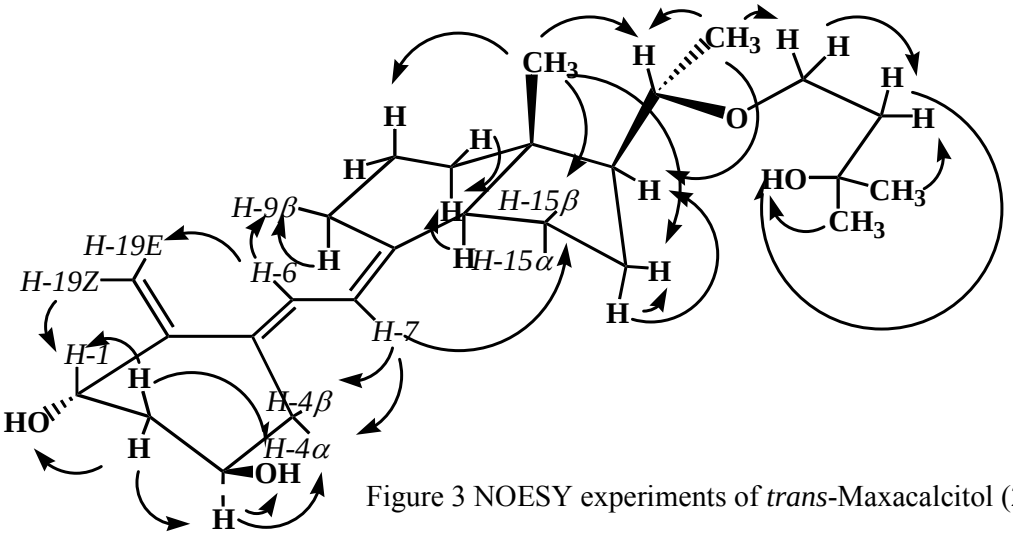


Figure 3 NOESY experiments of *trans*-Maxacalcitol (2)

In conclusion, we have obtained stereoselectively the *trans*-C5 isomer (**2**) of Maxacalcitol (**1**) without leaving the starting material through a Diels-Alder and retro-Diels-Alder sequence *via* a diastereomeric mixture of the sulforene intermediates (**3**). The differentiation-inducing effect[7] of the *trans*-C5 isomer (**2**) is about 1/10 of that of Maxacalcitol[8]. Presently biological evaluation of the *trans*-C5 isomer (**2**) is under investigation.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used without further purification. NMR spectra were measured on a JEOL EX-270 spectrometer at 270 MHz for ^{1}H and 67.8 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS at 0.00 for ^{1}H, and TMS at 0.0 for ^{13}C. Coupling constants (*J*) are reported in hertz. IR spectra were recorded on a JEOL JIR-6000 spectrophotometer as KBr pellets with a scan range of 4000-400 cm^{-1}. Ultraviolet spectra were measured on a HITACHI U3210 spectrometer.

Transformation of Maxacalcitol (1) into *trans*-C5-Maxacalcitol (2) :

(a) **Isomerization under sunlight** – Maxacalcitol (**1**) (500 mg, 1.19 mmol) was dissolved in acetone (200 mL) in a Pyrex round-bottom flask and the solution was stirred under sunlight at rt for 4 h. After evaporation of the solvent under reduced pressure, the residue was separated using a preparative HPLC (Kromasil ODS column, 5 μm, 50 mm I.D. × 301.5 mm, elution with 36% *aq*. MeCN) to give pure **2** (10 mg, 2.0%).

(b) **Isomerization through a cycloaddition sequence** –

(i) Cycloaddition Reaction – To Maxacalcitol (**1**) (5.23 g. 12.5 mmol) in a 200 mL round-bottom flask under nitrogen was introduced liquid sulfur dioxide (ca. 200 mL) and the suspension was stirred under reflux (~ –15 ºC) for 1 h, shaded off into yellowish brown solution. After evaporation of the excess sulfur dioxide at rt, the residue was dissolved in CH_2Cl_2 (20 ml) and the solution was evaporated under reduced pressure to leave the adduct (**3**) as a brown powder (6.24 g, quantitative) which was used for the next conversion without further purification.

(ii) Cycloreversion Reaction – A suspension of the adduct (**3**) obtained and $NaHCO_3$ (6.3 g, 75 mmol) in ethanol (120 mL) was refluxed for 4 h. After evaporation of the solvent under reduced pressure, the residue was extracted with AcOEt and THF. The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure to leave a crystalline solid which was recrystallized from AcOEt to give pure **2** (3.64 g, 70%), as colorless crystals. IR (KBr): γ 3367, 3080, 3047, 2966, 2939, 2875, 2833, 1643, 1626, 1446, 1410, 1373, 1317, 1263, 1221, 1147, 1126, 1103, 1093, 1049, 1028, 951, 889, 887, 833, 831, 773, 731, 727, 717, 687, 656, 596, 505, 471; UV nm (λmax : EtOH): 209 (12200), 273 (22200)

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