

*Supporting Information for*

# Selective Crystallization of Vitamin D<sub>3</sub> to Prepare Novel Conformational Polymorphs with Distinctive Chemical Stability

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## EXPERIMENTAL SECTION

**Materials.** Vitamin D<sub>3</sub> (VD<sub>3</sub>, form A) was purchased from J&K Chemical Ltd, with greater than 99% purity. All analytical grade solvents were purchased from Sinopharm Chemical Reagent Co., Ltd and used without further purification.

**Preparation of form B.** VD<sub>3</sub> (1.80 g) was dissolved in 30 mL of EtOH in a beaker at room temperature and then cooled down slowly to 0 °C. After about one night, colorless prism-shaped crystals of form B were harvested and dried under vacuum (1.65 g, 91.7% yield).

**Thermogravimetric analysis (TGA).** Thermogravimetric analysis was carried out in Netzsch TG 209 F3 equipment, using dry air with a nitrogen gas flow of 20 mL/min and a scan rate of 10 °C/min.

**Differential scanning calorimetry (DSC).** Differential scanning calorimetry (DSC) was performed with a PerkinElmer DSC 8500 instrument under nitrogen gas flow of 20 mL/min purge. Samples weighting 3–5 mg were heated in standard aluminum pans at scan rates from 5 to 10 °C/min. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment.

**Powder X-ray diffraction (PXRD).** PXRD patterns were obtained using a Bruker D8 Advance X-ray diffractometer (Cu K $\alpha$  radiation). The voltage and current applied were 40 kV and 40 mA respectively. Samples were measured in reflection mode in the 2 $\theta$  range 3–40° with a scan speed of 1.2 °/min (step size 0.025°, step time 1.0 s) using a LynxEye detector. Data were imaged and integrated with RINT Rapid, and the peaks are analysed with Jade 6.0 software from Rigaku. Calibration of the instrument was performed using Corindon (Bruker AXS Korundprobe) standard.

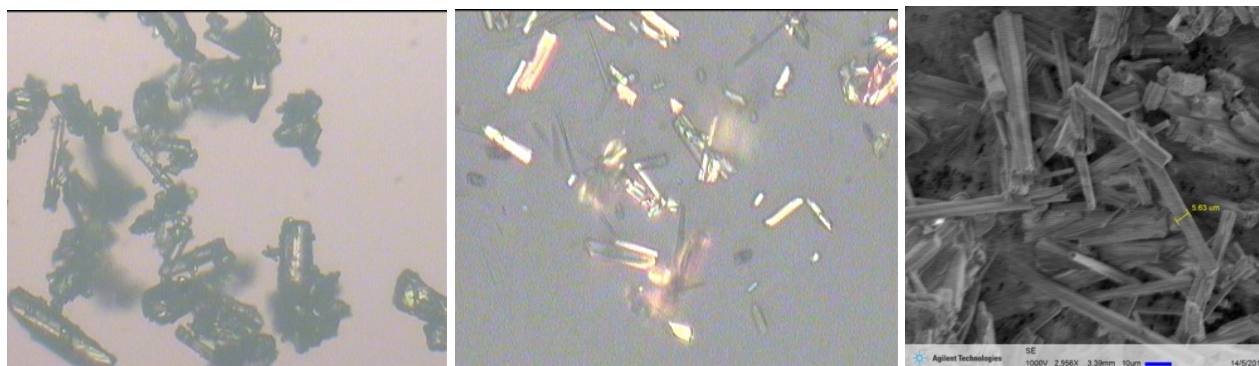
**Single crystal X-ray diffraction.** Single crystal X-ray diffraction of form B (0.15 × 0.10 × 0.10 mm<sup>3</sup>) was performed on a Bruker Apex II CCD diffractometer using Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) at 170 (2) K. The structures were solved by direct methods and refined with full-matrix least-squares difference Fourier analysis using SHELX-97 software. All non-hydrogen atoms were refined with anisotropic

displacement parameters, and all hydrogen atoms were placed in calculated positions and refined with a riding model. Data were corrected for the effects of absorption using SADABS.

**Solid-state  $^{13}\text{C}$  CP/MAS NMR.** Solid-state  $^{13}\text{C}$  cross-polarization/magic angle spinning (CP/MAS) spectra were collected on a Bruker AVANCE III-500MHz spectrometer (Bruker BioSpin, Germany), equipped with a 4 mm double-resonance MAS probe. A total sideband suppression frame was embedded into the conventional CP pulse sequence. The Hartmann-Hahn conditions of the CP experiment for acquiring  $^{13}\text{C}$  spectra were optimized by using adamantane.  $^{13}\text{C}$  NMR spectra were obtained at an 8 kHz MAS spinning speed with a contact time of 2.0 ms. Recycle delay times for forms A and B are 10 s. The  $^{13}\text{C}$  chemical shifts were externally referenced to tetramethylsilane ( $\delta = 0.0$  ppm).

**Dynamic vapor sorption (DVS).** The water sorption and desorption processes were measured on an Intrinsic DVS instrument from Surface Measurement Systems, Ltd. Samples were mounted on a balance, and studied over a humidity range from 0 to 95% RH, and then decreased to 0% RH at 25 °C. Each humidity step was made if less than a 0.02% weight change occurred over 10 min.

**Fluorescence.** Fluorescence spectroscopy measurements were carried out on Hitachi F-7000 spectrometer. Data were collected with excitation band passes set to 10 nm. Scan speed was 240 nm/min. Emission spectra were sampled with excitation wavelength 346 nm.

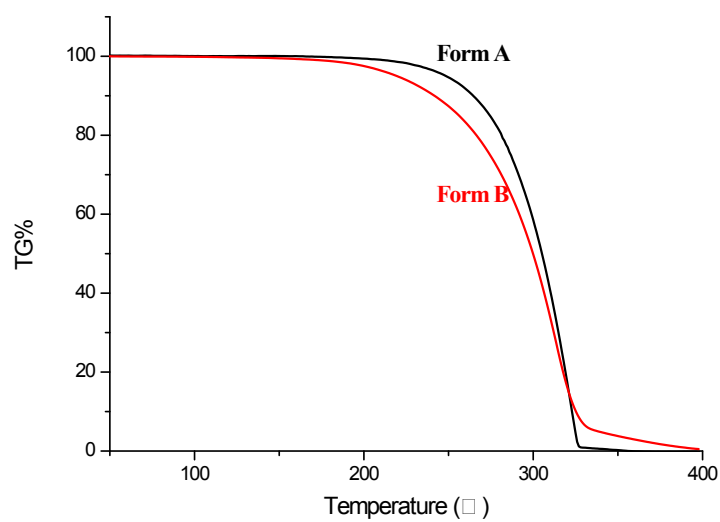


(a)

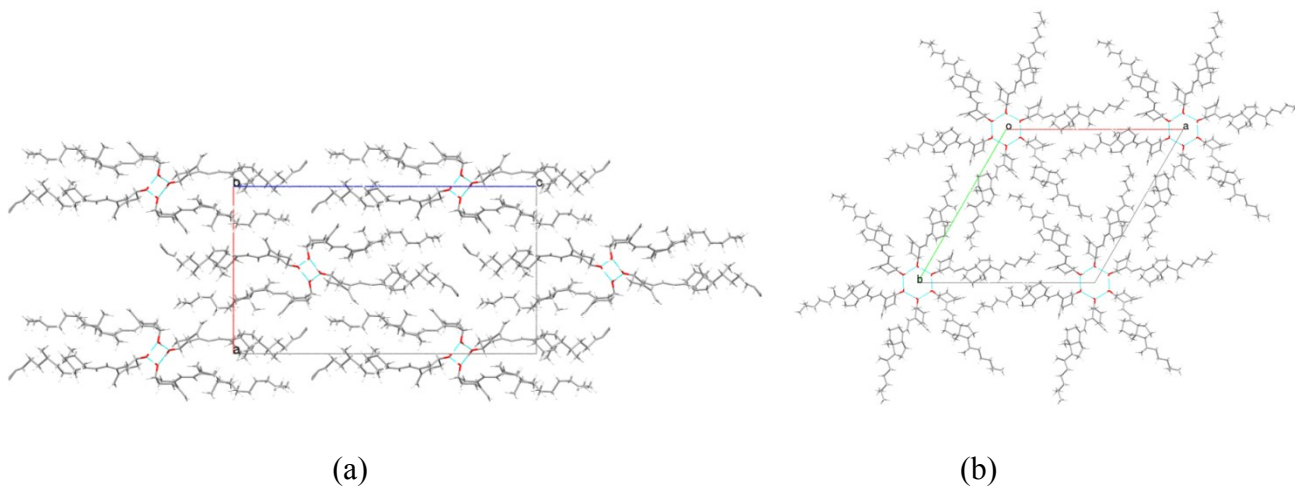
(b)

(c)

**Figure S1** Optical micrographs of forms A (a) and B (b), and SEM graph of form B (c)



**Figure S2** Comparison of TGA diagrams of forms A and B



(a)

(b)

**Figure S3** Packing diagrams of forms A (a) and B (b)

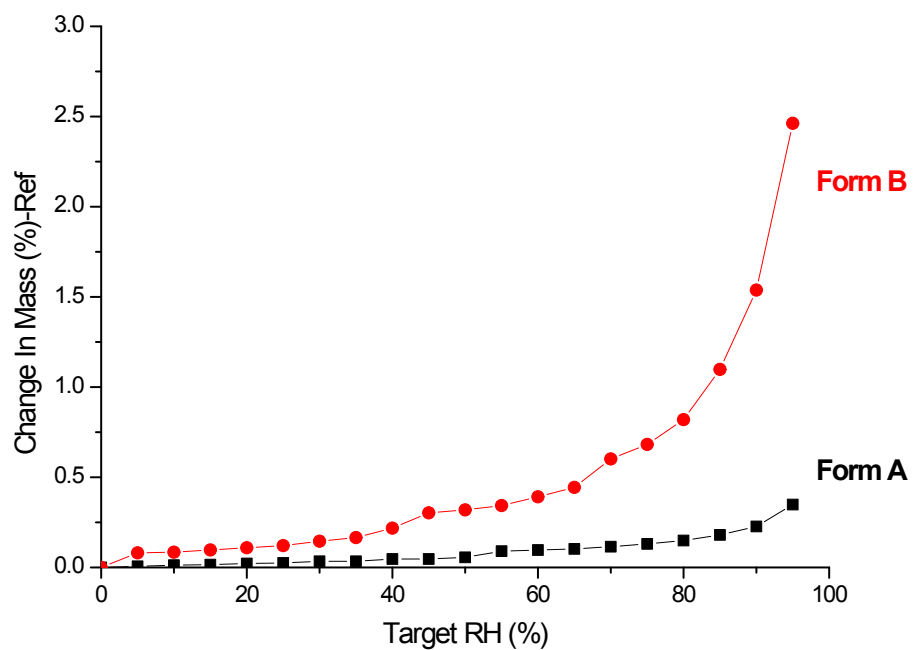


Figure S4 Dynamic vapor sorption isotherms of VD<sub>3</sub> forms A and B

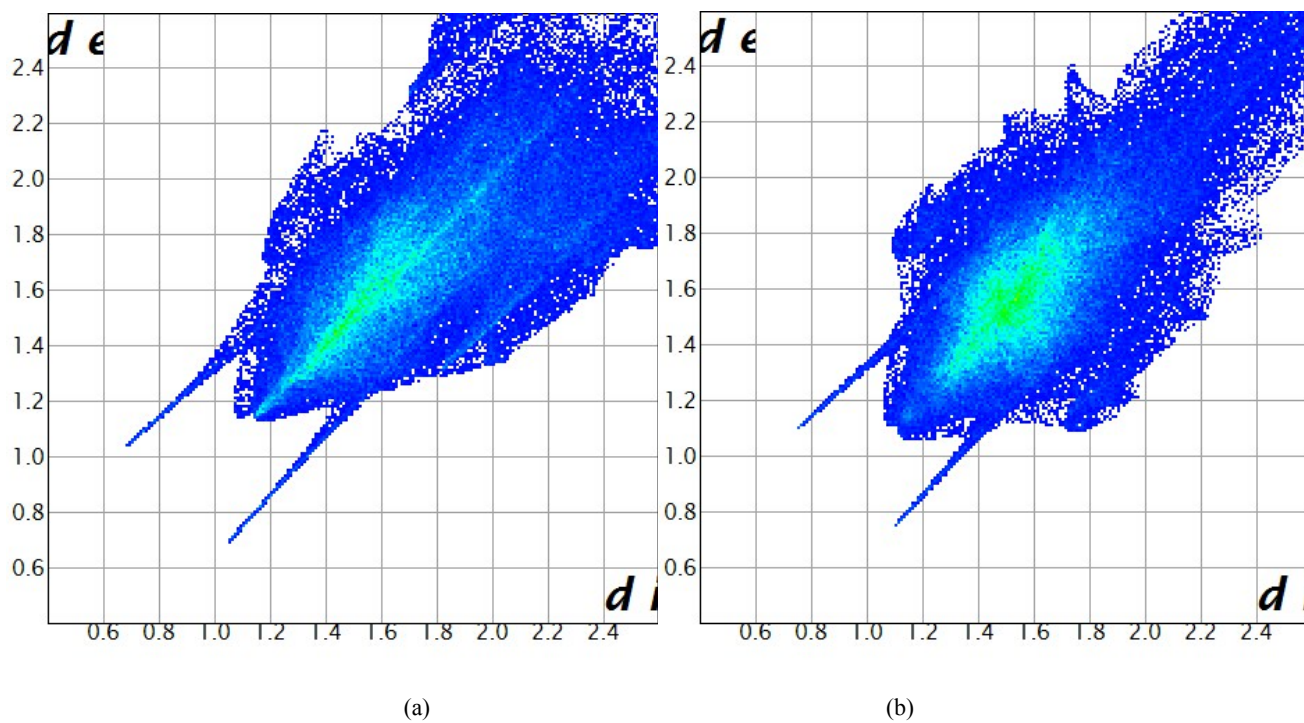
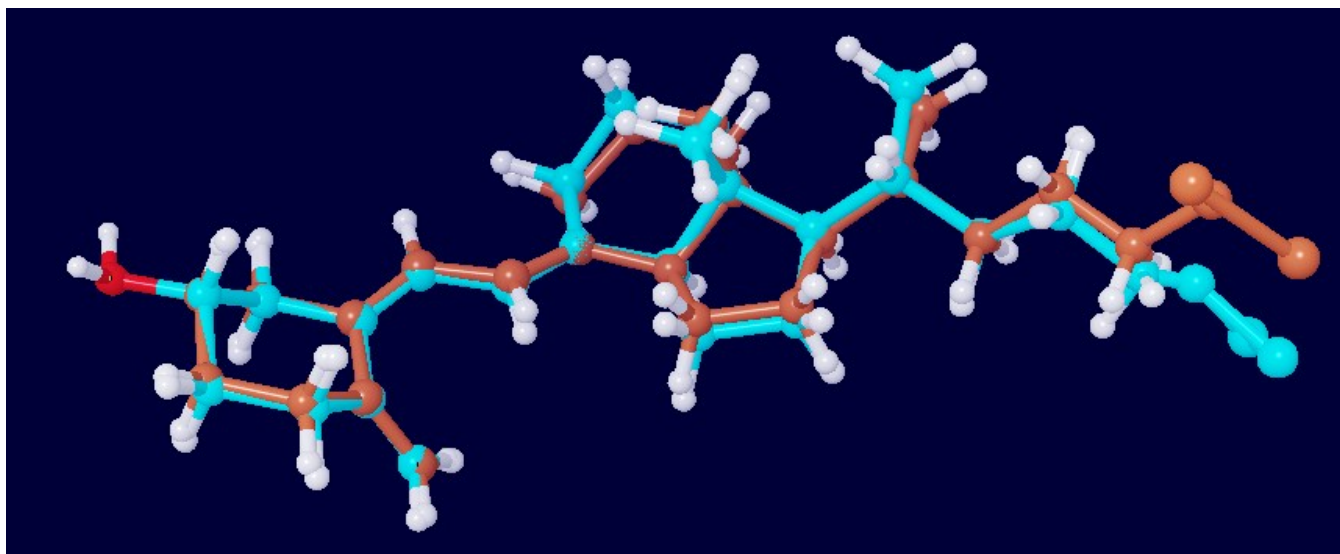


Figure S5 Hirshfeld fingerprint ( $d_i-d_e$ ) plots for  $\alpha$  conformer in forms (a) A and (b) B.



**Figure S6** Comparison of  $\alpha$  conformers found in form A (blue) and B (brown).

**Table S1** Crystallographic data for form B.

Form B	
Formula	C <sub>27</sub> H <sub>44</sub> O
Mr.	384.62
Crystal system	Hexagonal
Space group	<i>P</i> 6 <sub>5</sub>
Temperature (K)	170(2)
<i>a</i> (Å)	28.2798(11)
<i>b</i> (Å)	28.2798(11)
<i>c</i> (Å)	5.9321(3)
$\alpha$ (°)	90
$\beta$ (°)	90
$\gamma$ (°)	120
Cell volume (Å <sup>3</sup> )	4108.6(4)
Calc. density (g/cm <sup>3</sup> )	0.933
<i>Z</i>	6
$\lambda$ (Mo-K $\alpha$ )	0.71073
<i>S</i>	1.021
<i>R</i> <sub>1</sub>	0.066
<i>R</i> <sub>int</sub>	0.104
w <i>R</i> <sub>2</sub>	0.150

**Table S2** The NMR chemical shift for C3, 5, 6, 7, 8, 10, and 19.

No.	Solution NMR		Form A (ssNMR)		Form B (ssNMR)
	$\alpha$	$\beta$	$\alpha$	$\beta$	$\alpha$
3	70.21	66.82	70.61	67.37	70.29
5	137.59	135.57	138.04	136.09	138.69
6	119.69	121.62	120.21	122.16	121.18
7	120.29	117.05	120.86	117.62	121.18
8	139.16	140.14	140.63	139.66	140.63
10	145.84	147.62	148.09	146.47	148.09
19	111.60	111.83	112.11	112.11	112.11

**Table S3** Compared parameters of forms A and B

Form	A	B
Hydrogen bonding (Å)	2.707(0), 2.726(1)	2.822(7)
Calc. density (g/cm <sup>3</sup> )	0.99	0.93
MW	768	384
V of molecules (Å <sup>3</sup> )	422	422
V of cell (Å <sup>3</sup> )	5172	4109
$C_k$	65.3%	61.6%