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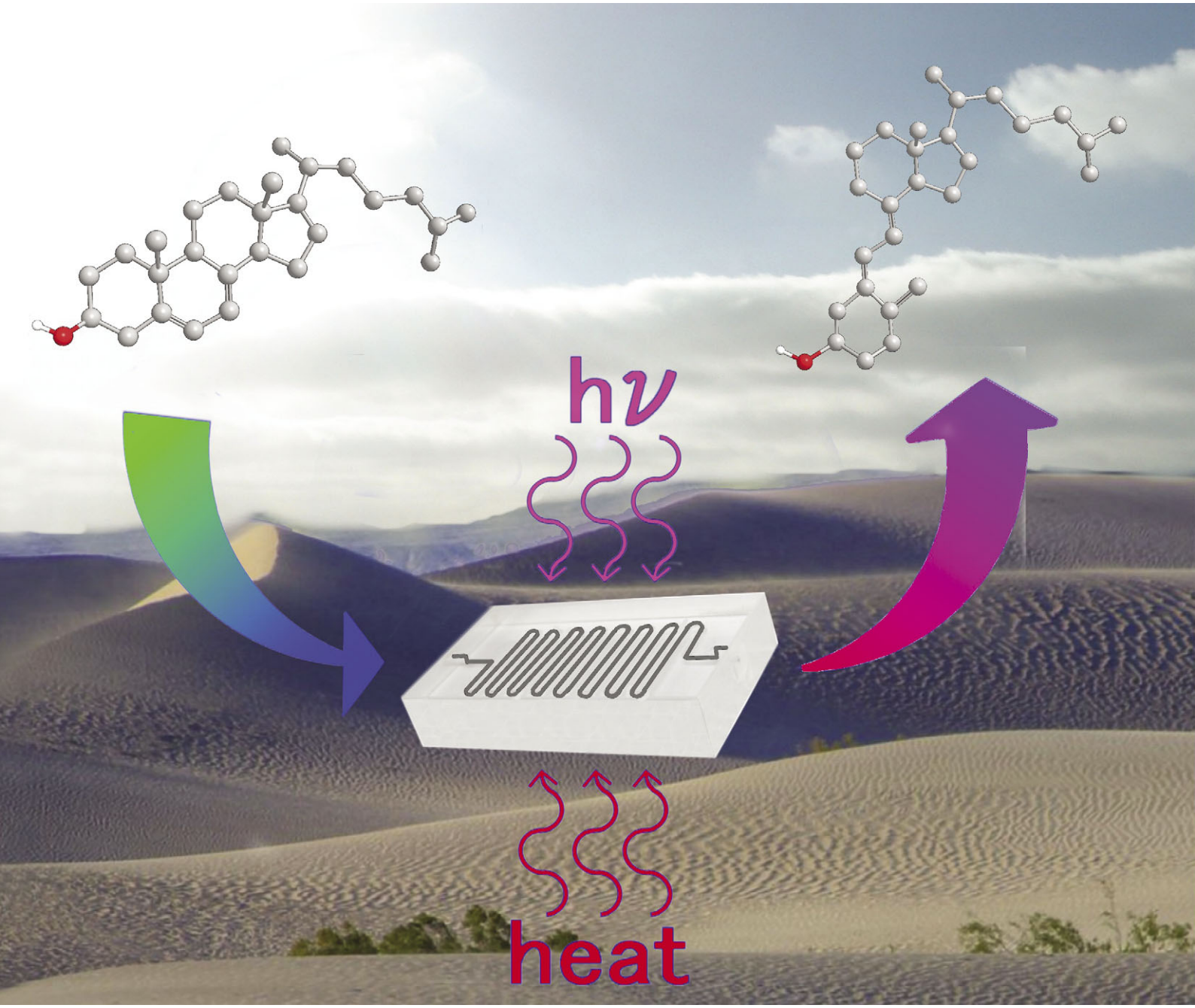

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Continuous-flow synthesis of vitamin D3

Continuous-flow synthesis of vitamin D_3†

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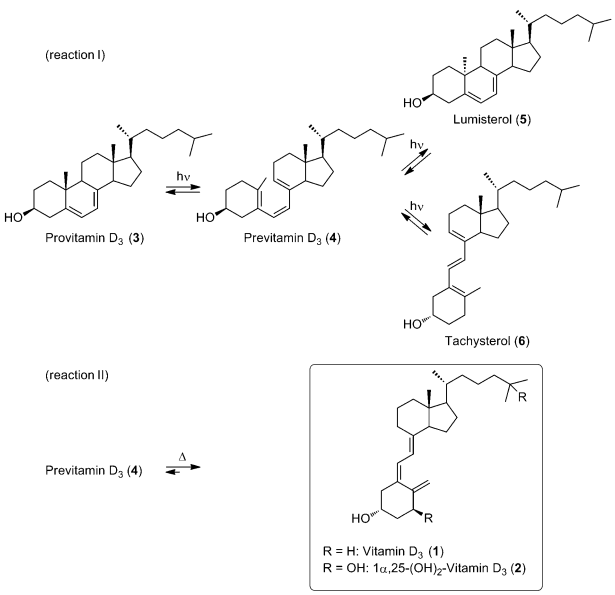
A highly efficient, two-stage, continuous-flow synthesis of vitamin D_3 from provitamin D_3 was achieved. The developed method afforded the desired product in high yield (HPLC-UV: 60%, isolated: 32%) and required neither intermediate purification nor high-dilution conditions.

Vitamin D_3 (**1**) is metabolized sequentially in the liver and kidney into its hormonally active form, 1α,25-$(OH)_2$-vitamin D_3 (**2**), which has a broad spectrum of biological activities such as cell differentiation and regulation of calcium metabolism and immune function.[1,2] The two-step conversion of provitamin D_3 (**3**) to vitamin D_3 (**1**) *via* previtamin D_3 (**4**) is important[3,4] not only for the synthesis of biologically active analogues[5,6] of vitamin D_3, but also for its commercial preparation (Scheme 1). However, the overall yield of vitamin D_3 (**1**) after thermal-isomerization (reaction (II)) of previtamin D_3 (**4**) is generally low because the photo-isomerization step is not selective (reaction (I)) and because separation of the products is difficult.[7–10] Because previtamin D_3 (**4**) has an absorption wavelength that is similar to that of provitamin D_3 (**3**), the undesired products lumisterol (**5**) and tachysterol (**6**) result from the equilibrium between the products (reaction (I)).[3,11] The over-all yield of the current industrial preparation of vitamin D_3 is less than 20%.[12]



Scheme 1 Two-step conversion of provitamin D_3 (**3**) to vitamin D_3 (**1**).

Our solution to this problem was to simultaneously perform the photo- and thermal-reactions in a microreactor.[13–21] We anticipated that the previtamin D_3 (**4**) produced from photo-isomerizations would be smoothly converted into vitamin D_3 (**1**) through thermal-isomerization. Thus, the equilibrium in the photo-isomerization would shift to produce more previtamin D_3 (**4**). Photo-microreactors have advantages over conventional batch reactors.[22–24] Namely, photo-microreactors exhibit improved light-penetration efficiency due to the thinness of the reaction mixture in the microspace. We used a microreactor that enabled simultaneous photo- and thermal-reactions to synthesize vitamin D_3 (**1**). Herein, we report the first micro-flow synthesis of vitamin D_3 (**1**) using a high-intensity and economical light source, *i.e.*, a high-pressure mercury lamp, with no intermediate purifications. Our report is also the first to describe photo- and thermal-reactions in a single microreactor to afford the desired vitamin D_3 in high yield.

We planned to examine the two-stage irradiation method[3,25] shown in Fig. 1. Reportedly, a two-stage method that uses a laser and/or a sensitizer in batch reactors affords the desired vitamin D_3 in good yield.[26–28] We anticipated that the mixture of previtamin D_3 (**4**) and tachysterol (**6**) prepared from provitamin D_3 (**3**) using the photo-microreactor (313–578 nm) would be converted into the desired vitamin D_3 (**1**) using the photo- and thermal-microreactor (360 nm, 100 °C). Consequently, the equilibrium for the photo-isomerization of

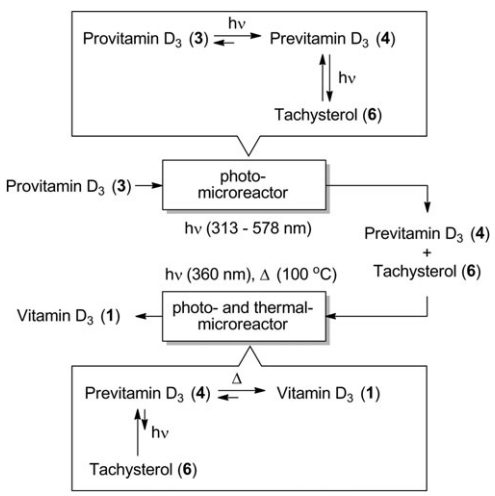


Fig. 1 Micro-flow synthesis of vitamin D_3 (**1**) by way of the two-stage method.

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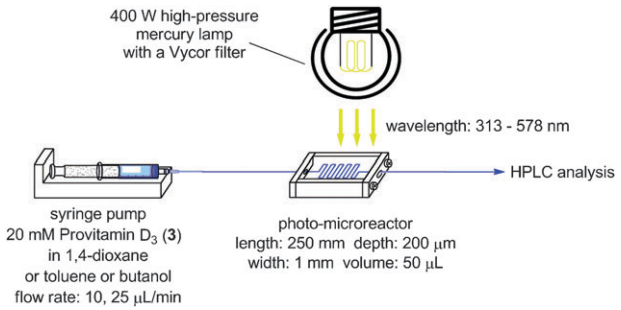

Fig. 2 Photolysis of provitamin D_3 (**3**) using the photo-microreactor.

tachysterol (**6**) to previtamin D_3 (**4**) would shift to produce more previtamin D_3 (**4**).

Photo-isomerization of provitamin D_3 (**3**) using a micro-reactor has not been previously reported. Thus, we first examined the micro-flow photo-isomerization in several organic solvents by using a 400 W high-pressure mercury lamp with a Vycor filter (Fig. 2). In a continuous-flow synthesis that requires no intermediate purification steps, solvents used in prior steps must be compatible with downstream reactions. Since the thermal-isomerization of previtamin D_3 (**4**) to vitamin D_3 (**1**) proceeds well over *ca.* 80 °C, the solvents toluene (bp 110 °C), butanol (bp 117 °C) and 1,4-dioxane (bp 101 °C) were examined. The microreactor was made of quartz and had a channel that was 200 μm deep, 1 mm wide, and 250 mm long with a volume of 50 μL.[29] A 20 mM solution of provitamin D_3 (**3**) was introduced with a syringe pump[29] at flow rates of 10 or 25 μL min^{-1}. The obtained reaction mixtures were then analyzed by HPLC on a Senshu Pak PEGASIL Silica-3301-N (8Φ × 300 mm) column.

Table 1 Composition of products obtained from the photolysis of provitamin D_3 (**3**)

Entry	Solvent	Flow rate/ μL min^{-1}	Yield[c] (%)			
			3	**4**	**5**	**6**
1	1,4-Dioxane	10[a]	5	48	9	38
2	1,4-Dioxane	25[b]	7	45	9	39
3	Toluene	10[a]	10	53	13	24
4	Toluene	25[b]	16	50	11	23
5	Butanol	10[a]	7	55	12	26
6	Butanol	25[b]	20	47	11	22

[a] Residence time (RT) in the photo-microreactor: 5 min. [b] RT in the photo-microreactor: 2 min. [c] The yields were calculated based on the relative UV absorption after allowance was made for the extinction coefficient at 282 nm.

The compounds were identified by UV monitoring at 282 nm. The composition of products was calculated based on the relative UV absorption after allowance was made for the extinction coefficient at the monitoring wavelength.

Fortunately, the photo-reaction in 1,4-dioxane afforded the desired previtamin D_3 (**4**) and tachysterol (**6**) in a combined yield of >80% (Table 1, entries 1 and 2).[30] In other solvents, the yields of the two products were slightly lower (entries 3–6). It should be noted that the generation of undesired lumisterol (**5**) was suppressed (<10%), and the desired compounds **4** and **6** were obtained in high yields even though the concentration of the reaction mixture (20 mM) was somewhat greater than that seen under conventional photo-reaction conditions (*ca.* 0.1 mM).[26,27,31]

We prepared a continuous-flow system (Fig. 3). Two micro-reactors were connected with PEEK tubing. The first one was irradiated with 313–578 nm light (400 W high-pressure mercury lamp with a Vycor filter). The second one was irradiated with 360 nm light (400 W high-pressure mercury lamp with a Vycor filter and a glass UV filter) and it was put on hot oil (100 °C). Then, 20 or 30 mM solutions of provitamin D_3 (**3**) in 1,4-dioxane were introduced with a syringe pump at flow rates of 5, 10 or 25 μL min^{-1}. The desired vitamin D_3 (**1**) was obtained in modest yields when the 20 mM solution was used (Table 2, entries 1–3). However, to our delight, vitamin D_3 (**1**) was obtained in excellent yield (HPLC-UV: 60%) when the higher concentration of provitamin D_3 (**3**) (30 mM) was used at the lowest flow rate (*i.e.*, 5 μL min^{-1}) (entry 4). After chromatographic separation, the desired vitamin D_3 (**1**) was obtained in 32% yield employing the conditions described in entry 4. To the best of our knowledge, this is the highest yield ever achieved without the use of a laser,[26,27,31] a sensitizer[32] or a filter compound.[28]

In summary, we successfully achieved two-stage continuous-flow synthesis of vitamin D_3 (**1**) using a high-intensity and economical light source, *i.e.*, a high-pressure mercury lamp. This is the first application of a micro-flow system to the synthesis of vitamin D_3 (**1**) from provitamin D_3 (**3**). Our report is also the first demonstration of simultaneous photo- and thermal-reactions in a single microreactor, which enabled the high conversion of tachysterol (**6**) to vitamin D_3 (**1**) *via*

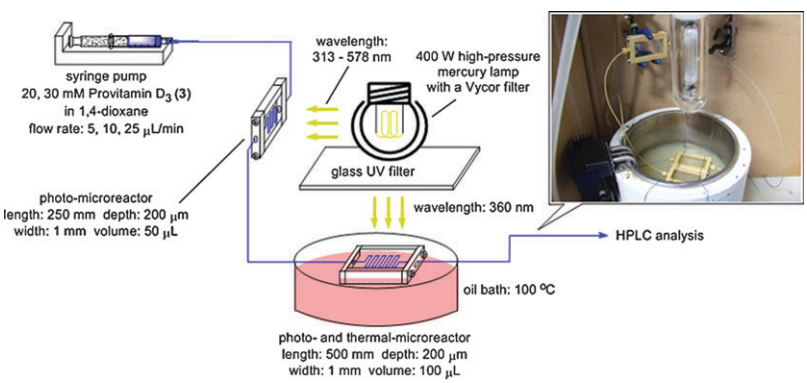

Fig. 3 Two-stage, continuous-flow synthesis of vitamin D_3 (**3**) using two microreactors.

Table 2 Composition of products obtained from the two-stage, continuous-flow reaction

Entry	Conc./mM	Flow rate/ μL min^{-1}	Yield[e] (%)					
			1	**3**	**4**	**5**	**6**	**7**[d]
1	20	5[a]	38	4	12	33	12	1
2	20	10[b]	46	4	17	7	22	4
3	20	25[c]	38	4	15	6	36	1
4	30	5[a]	60	9	12	8	6	5
5	30	10[b]	49	5	14	6	24	2
6	30	25[c]	40	4	12	7	36	1

[a] RT in the photo-microreactor: 10 min. RT in the photo- and thermal-microreactor: 20 min. [b] RT in the photo-microreactor: 5 min. RT in the photo- and thermal-microreactor: 10 min. [c] RT in the photo-microreactor: 2 min. RT in the photo- and thermal-microreactor: 4 min. [d] Undesired *trans*-vitamin D_3 (**7**) was generated from the photo-isomerization of vitamin D_3 (**1**). [e] The yields were calculated based on the relative UV absorption after allowance was made for the extinction coefficient at 282 nm.

previtamin D_3 (**4**). Finally, the desired vitamin D_3 (**1**) was obtained in excellent yield (HPLC-UV: 60%, isolated: 32%). To the best of our knowledge, this is the highest yield ever achieved without the use of a laser, a sensitizer or a filter compound. One of the advantages of using microreactors is the ease of scaling up. It should be possible to scale up our developed process by either continuous running or by the numbering up of the microreactors. It should be noted that the continuous micro-flow synthesis of vitamin D_3 (**1**) did not require the purification of intermediates or high-dilution conditions, thereby reducing waste.

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30 The photo-isomerization of provitamin D_3 (**3**) using conventional batch reactor (concentration of provitamin D_3 (**3**): 20 mM, reaction time 150 min) afforded the desired mixture of previtamin D_3 (**4**) and tachysterol (**6**) in 23% combined yield. A large amount of provitamin D_3 (**3**) was recovered (50%) and undesired lumisterol (**5**) was generated (25%). This result clearly shows the advantages of the flow condition over the batch condition.
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