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Selective capture of 1α,25-$(OH)_2$-previtamin D_3 utilizing polymer-supported trialkylsilyl triflate in the synthesis of 1α,25-$(OH)_2$-vitamin D_3

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Abstract—Catch and release method utilizing polymer-support was investigated in the separation of 1α,25-$(OH)_2$ pre- and provitamin D_3. Polymer-supported alkyldiisopropylsilyl triflate selectively captured the previtamin D_3 from a 26:74 mixture of pre- and provitamin D_3 produced by photoisomerization of provitamin D_3.
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The hormonally active metabolite of vitamin D_3, 1α,25-$(OH)_2$-vitamin D_3 (**1**), has a broad spectrum of biological activities such as cell differentiation, regulation of calcium metabolism and immune system.[1] Photo- and thermal-isomerization of provitamin D_3 are conventional methods for the production of vitamin D_3 derivatives due to the facile availability of the starting compounds.[2,3] In this synthesis, photo-isomerization of 1α,25-$(OH)_2$-provitamin D_3 (**2**) provides 1α,25-$(OH)_2$-previtamin D_3 (**3**), which undergoes subsequent thermal-isomerization leading to 1α,25-$(OH)_2$-vitamin D_3 (**1**). The problem, however, is the low yield of the desired **1** due to lack of selectivity in the photo-isomerization step and difficulty of the separation of the isomers produced. Normally, conversion of **2** would give not only the desired **3** but also tachysterol **4** and lumisterol **5** through the equilibrium of the products. Therefore, extensive studies have been reported to resolve this problem.[3,4]

Our solution for the synthesis of 1α-(OH) derivatives is the development of a versatile method for the separation from a mixture of pro- and previtamin D_3 derivatives **2** and **3** produced in the early stage of the photo-isomerization. In this paper, we wish to report a catch and release method[5] by selective capture of the previtamin D_3 **3** utilizing polymer-supported trialkylsilyl triflate.

We focused on the steric hindrance of a hydroxy group at the Cl position. The 1α-OH group of provitamin D_3 **2** has an axial orientation and is covered by a steroid skeleton, whereas that of previtamin D_3 **3** would be less hindered because the B-ring is expanded by photo-isomerization. Therefore, it is expected that the less hindered 1α-OH group of **3** can be selectively captured from a mixture of **2** and **3** by polymer-supported trialkylsilyl triflate.[6] Subsequently, the previtamin D_3 **3** could be released from the polymer-support by treatment with acid.[7] We investigated the selective capture utilizing three sterically distinct alkyl-substituted silyl triflates on polymer-supports **6**, which are employed for simple purification (Scheme 1).

Preparation of **10** is shown in Scheme 2. Tosylation of **7**[8] using DMAP, followed by hydrolysis of methyl carbonates with KOH afforded diol **8** in 92% yield. Selective protection of the C-3 hydroxy group with TESCl and imidazole at −78 °C provided **9**. Alkylation of tosylate **9** with 3-methyl-3-(trimethylsilyl)butylmagnesium bromide at the C-22 position in the presence of copper catalyst[7] furnished the desired **10** in 54% overall yield.[9]

Photo-isomerization of **10** was carried out in THF using high pressure mercury lump with Vycor filter at −8 °C for 30 min. A mixture of previtamin D_3 produced and the remaining starting provitamin D_3 (**11**:**10** = 26:74, HPLC ratio),[10] was treated with polystyrene based silyl triflate resin **6** (1.3 equiv for previtamin D_3) and 2,6-lutidine at room temperature for 12 h. The resin was

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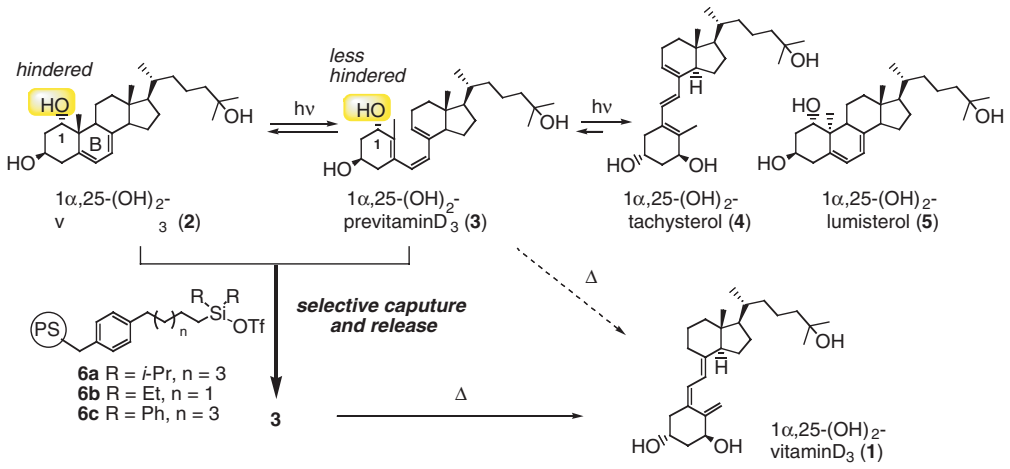
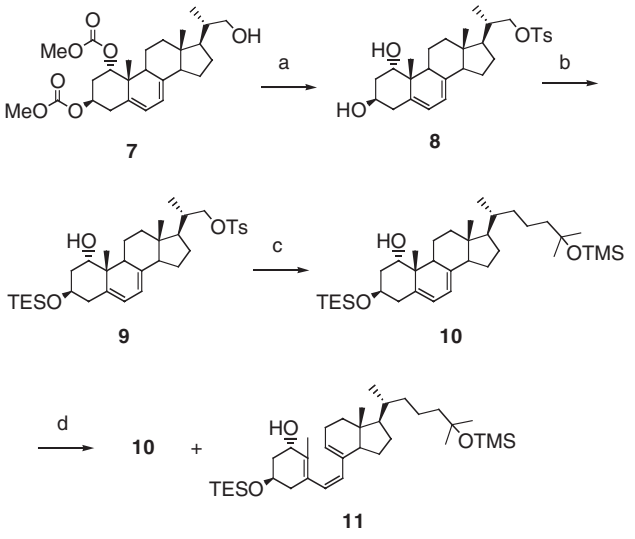


Scheme 1. Photo- and thermal-isomerization of provitamin D_3 to vitamin D_3.



Scheme 2. (a) (i) TsCl, DMAP, CH_2Cl_2, rt, 4 h; (ii) KOH, MeOH–THF (1:1), 45 °C. (b) TESCl, imidazole, CH_2Cl_2, −78 °C. (c) $BrMgCH_2CH_2C(CH_3)_2OTMS$, CuBr·$Me_2S$ (12 mol%), THF, rt, 1 h. (d) hν, THF, −8 °C.

filtered and washed with CH_2Cl_2 and the unreacted mixture was recovered from the filtrate. Release of the captured alcohols was carried out by treatment with HF·Py at room temperature for 12 h. The cleavage solution obtained was analyzed by HPLC to determine the ratio of the captured previtamin D_3 and provitamin D_3. The results were depicted in Figure 1. PS-DIPS resin **6a** (R = *i*-Pr, 0.6 mmol/g)[11] captured the products totaling 17% yield with high selectivity (**3**:**2** = 92:8, Fig. 1a).[12] This catch and release method was repeated for the recovered mixture to afford another 4% of **3** and **2** in a ratio of 82:18. Alternatively, **3** was obtained in overall 21% (90% purity, 81% yield based on the 26:74 mixture of **11** and **10**), and **10** (76%) was recovered from the filtrate. The **3** obtained by the catch and release method was heated at 80 °C to provide 1α,25-$(OH)_2$-vitamin D_3 (**1**) in quantitative yield.[12] On the other hand, commercially available PS-DES™ resin **6b** (R = Et, 0.96 mmol/g),[13] captured not only previtamin D_3 but also provitamin D_3 (**3**:**2** = 55:45, Fig. 1b) in 34% yield (90% based on the used amount of **6b**). Presumably, steric effect of the isopropyl group rather than the ethyl group on a silicon atom is important in this selection. This application using PS-DPS resin **6c** (R = Ph, 0.65 mmol/g),[11] provided a complex mixture of unknown compounds (data now shown).

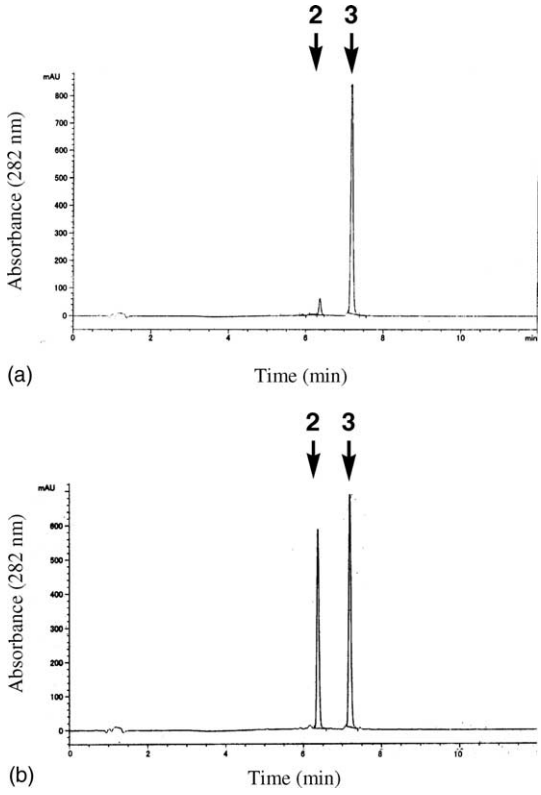


Figure 1. Analytical HPLC of the catch and release product was performed using Inertsil™ ODS-3 3 μm, 4.6×75 mm, and linear gradients of 0.1% formic acid in acetonitrile and 0.1% aqueous formic acid were run at 1.0 mL/min flow rate from 1:9 for 1 min, 1:9 to 1:0 over 4 min, and then 1:0 for 7 min. Figure 1a (above) result using PS-DIPS resin **6a**, **3**:**2** = 92:8. Figure 1b (below) result using PS-DES resin **6b**, **3**:**2** = 55:45.

In summary, we have demonstrated the selective capture of 1α,25-$(OH)_2$-previtamin D_3 (**3**) utilizing alkyldiisopropylsilyl triflate on polymer-support. Since thermal-isomerization of previtamin D_3 affords vitamin D_3, this catch and release method can be an important protocol in the synthesis of 1α,25-$(OH)_2$-vitamin D_3.

Acknowledgements

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References and notes

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9. Compound **10**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.62 (br d, $J = 3.6$ Hz, 1H), 5.39 (m, 1H), 4.05 (m, 1H), 3.77 (br s, 1H), 1.20 (s, 6H), 0.99 (d, $J = 7.6$ Hz, 3H, f), 0.96 (t, $J = 7.9$ Hz, 9H), 0.88 (s, 3H), 0.63 (q, $J = 7.9$ Hz, 6H), 0.61 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.6, 137.1, 120.9, 115.1, 74.3, 73.9, 60.5, 56.1, 54.9, 45.4, 43.1, 42.8, 40.5, 39.3, 37.6, 36.5, 36.3, 30.0, 28.3, 23.2, 21.0, 20.7, 18.9, 16.5, 12.1, 7.3, 5.3, 2.8.
10. In this conversion, 1α,25-$(OH)_2$-tachysterol (**4**) and 1α,25-$(OH)_2$-lumisterol (**5**) were not formed more than 5%. Photolysis of 1α-OH free provitamin D_3 is faster than that of trialkylsilyl protected ethers Okabe, M.; Sun, R.-C.; Wolff, S. *Tetrahedron Lett.* **1994**, *35*, 2865–2868.
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