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Technical Notes

An Efficient Synthesis of a Key Intermediate for the Biologically Active Vitamin D Analogue, Seocalcitol

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Abstract:

In the key synthetic step in the manufacture of the key intermediate for the biologically active vitamin D analogue, seocalcitol, a more practical and attractive procedure is achieved using the commercially available EtMgBr and $CeCl_3$, resulting in 79% yield. The key intermediate is synthesised from vitamin D_2 in 10 steps with only three isolations, giving 21% overall yield.

Introduction

The hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (calcitriol) (Figure 1), has a wide range of activities, including cell-differentiating and antiproliferative activities in addition to its classical role in calcium homeostatis, and has been utilised to develop therapeutic agents for cancer, psoriasis, and osteoporosis. Most of the analogues synthesised thus far are modified in the side chain. Among them, seocalcitol (**1**) (Figure 1) has been shown to be more potent than 1α,25-dihydroxyvitamin D_3 in inhibiting proliferation, stimulating differentiation, and inducing apoptosis in a number of different cell types, including cancer cells. Despite being more potent than 1α,25-dihydroxyvitamin D_3 with respect to its cell regulatory effects, **1** displays weaker calcemic effects. These characteristics make **1** a potentially useful compound for the treatment of different forms of cancer. A phase I study with **1** in patients with advanced breast or colon cancer has already been carried out, and more clinical trials evaluating the clinical effectiveness of **1** in other types of cancer are in progress.[1a] Clinical evaluations of **1** have mainly focused on establishing a maximal tolerated dose in cancer patients. Early results confirm that the low calcemic activity observed in animals can be reproduced in the clinic. Furthermore, **1** has been shown to induce regression of tumours, especially in hepatocellular carcinoma where a couple of complete responses have been obtained. In conclusion, the development of **1** as an anti-cancer drug holds promise. However, its final evaluation must await the completion of ongoing controlled phase III clinical trials.[1b]

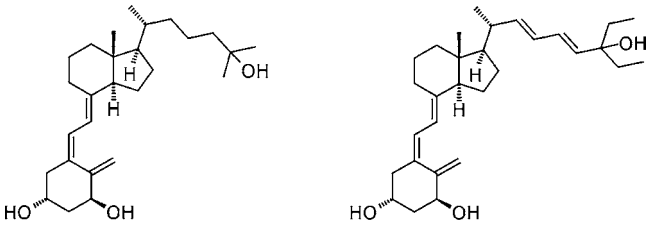

Figure 1.

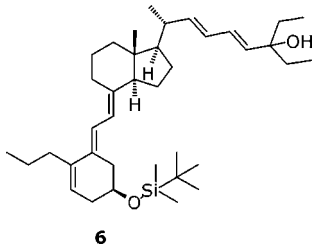

Figure 2.

Results and Discussion

The synthesis of the key intermediate **2** prior to the initiation of commercial production of seocalcitol is illustrated in Scheme 1. The aldehyde **3** is conveniently accessible by the route described in detail by Calverley[2] in 36% yield and the 2,4-dienoate **4** is obtained by Wittig olefination as described by Binderup et al.[3,4] in 73% yield.

Because of the importance of optimising the existing synthesis of the key intermediate **2** prior to the initiation of commercial production, the nucleophilic addition of a Grignard or organolithium reagent to the α,β-unsaturated carbonyl group of the intermediate **4** has received special attention throughout the years.

The nucleophilic addition of a Grignard or organolithium reagent to the α,β-unsaturated carbonyl group of **4** is accompanied by a competing conjugate 1,4-addition (**5**). This side reaction, which is mainly due to the high basicity and oxidation potential of the Grignard and organolithium reagents, can sometimes take over the normal 1,2-addition process (**2**), resulting in low yields of the desired products[5,6] (Scheme 2).

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(1) (a) Hansen, C. M.; Maenpaa, P. H. *Biochem. Pharmacol.* **1997**, *54*, 1173−1179. (b) Hansen, C. M.; Hamberg, K. J.; Binderup, E.; Binderup, L. *Curr. Pharm. Des.* **2000**, *6*, 803−828.

(2) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609−4619.

(3) Binderup, E.; Calverley, M. J.; Binderup, L. Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application. In *Proceedings of the 8th Workshop on Vitamin D, July 5−10, Paris*; 1991; pp 192−193.

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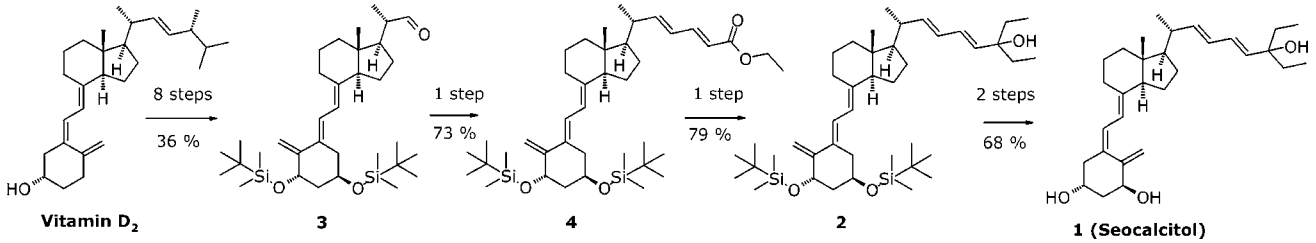
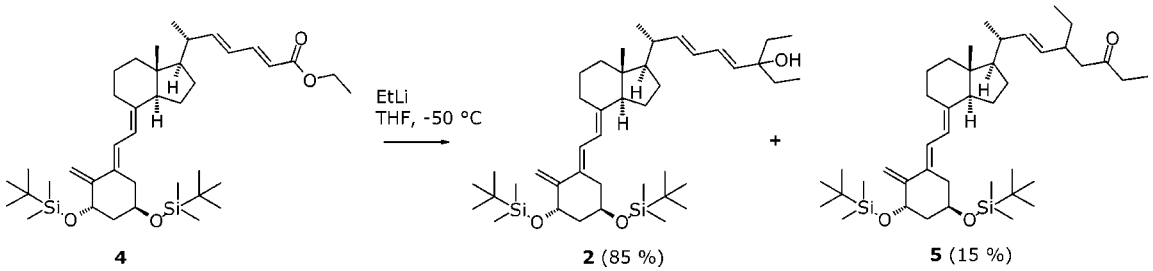
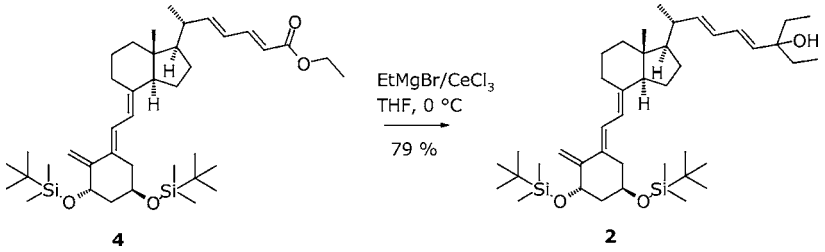
Scheme 1



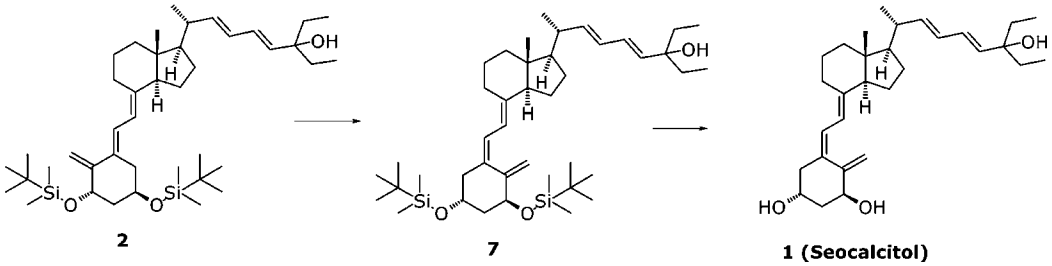
Scheme 2



Scheme 3



Scheme 4



Furthermore if the temperature exceeds −50 °C, EtLi will attack the exocyclic double bond in the A-ring to give the byproduct **6** (Figure 2).

Thus, by substituting the unstable EtLi (−50 °C) with the commercially available EtMgBr and $CeCl_3$ (0 °C), which is capable of retarding 1,4-addition (**5**) to yield the tertiary allyl alcohol **2** as the major product, a more practical and attractive procedure for commercial production of **2** appears due to higher temperature, higher yield (79%), facilitated workup, and improved impurity profile[7] (Scheme 3).

Clean photoisomerisation of **2** to the oily (5*Z*)-vitamin derivate **7**, followed by removal of the alcohol protective groups, completed the synthesis of the crystalline vitamin D analogue **1** in 68% yield[3,4] (Scheme 4).

Spectroscopic data: *compound* ***4*** *1(S),3(R)-bis(tert-butyldimethylsilyloxy)-20(R)-(4-ethoxycarbonylbuta-1′(E),3′(E)-dien-1′-yl)-9,10-secopregna-5(E),7(E),10(19)-triene*: $C_{40}H_{68}O_4Si_2$: Calcd C 71.80, H 10.24; found C 71.18, H 10.11. MW: 669.16 g/mol. ^{1}H: 0.05(12H,m), 0.56(3H,s), 0.85-(9H,s), 0.89(9H,s), 1.07(3H,d, J = 6.6), 1.28(3H, J = 7.2), 1.2−2.3(15H,m), 2.54(1H,dd, J = 14.1 and 5.0), 2.87(1H,-dd, J = 11.9 and 2.8), 4.18(2H,q, J = 3.7), 4.20(1H,m), 4.52-(1H,m), 4.93(1H,m), 4.97(1H,m), 5.77(1H,d, J = 15.3), 5.81(1H,d, J = 11.3), 5.98(1H,dd, J = 15.1 and 8.4), 6.11-

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(7) Typical procedure: anhydrous $CeCl_3$ (250.0 g) is placed with dry THF (3.2 L) in a dry, three-necked 10-L round-bottomed flask under N_2 at room temperature and stirred vigorously overnight. The flask is immersed in an ice bath, and EtMgBr in THF (1.0 M, 1.1 L) is added over 30 min. After stirring for 1.5 h at 0 °C, **4** (160.0 g) is added in portions. The reaction is checked by HPLC. The reaction mixture is treated with H_2O (2.0 L). The product is extracted with hexane (2.0 L), and the combined extracts are washed with aqueous $NaHCO_3$ (2 × 3.0 L) and aqueous NaCl (2 × 3.0 L). The solvent is evaporated to leave a clear yellow oil (235 g). The residue is dissolved in hexane (1.0 L) and subjected to preparative HPLC and crystallised from MTBE (320 mL) and MeOH (1400 mL) to give the addition product **2** in 79% yield. Mp 84−85 °C, $C_{42}H_{74}O_3Si_2$: Calcd C 73.84, H 10.92; found C 73.72, H 11.00. MW: 683.2. Disposal consideration of $CeCl_3$: the material should be dissolved in water or acid solution before disposal.

(1H,dd, $J = 15.1$ and 10.5), 6.44(1H,d, $J = 11.3$), 7.23(1H,-dd, $J = 15.4$ and 10.5). ^{13}C:167.1, 153.5, 150.1, 145.2, 142.6, 135.4, 126.0, 121.3, 119.0, 116.4, 106.4, 70.0, 67.0, 59.9, 56.1, 55.7, 45.9, 43.8, 40.4, 40.2, 36.4, 28.7, 27.4, 25.7, 25.6, 23.3, 22.1, 19.7, 18.1, 17.9, 14.1, 12.1, −4.9, −5.0, −5.08, −5.10. Exact mass for $C_{34}H_{52}O_3Si$ ($M^+ - C_6H_{16}OSi$) requires *m*/*z* 536.3686, found *m*/*z* 536.3682.

Compound ***2*** *1(S),3(R)-bis(tert-butyldimethylsilyloxy)-20-(R),5′-ethyl-5′-hydroxyhepta-1′(E),3′(E)-dien-1′-yl)-9,10-seco-opregna-5(E),7(E),10(19)-triene*: λ_{max} 232 nm ($\epsilon = 37350$), λ_{max} 269.5 nm ($\epsilon = 26900$). ^{1}H: 0.06(12H,m), 0.56(3H,s), 0.86(9H,s), 0.89(9H,s), (0.86(6H,t), 1.05(3H,d, $J = 6.6$), 1.20−2.20(19H,m), 2.30(1H,bd), 2.56(1H,dd), 2.87(1H,m), 4.21(1H,m), 4.53(1H,m), 4.94(1H,m), 4.98(1H,m), 5.52(1H,-dd, $J = 15.3$), 5.54(1H,dd, $J = 15$ and 8.6), 5.82(1H,d, $J = 11.4$), 5.97(1H,dd, $J = 15$ and 10.3), 6.15(1H,dd, $J = 15$ and 10.3), 6.45(1H,d,$J = 11.4$). ^{13}C: 153.5, 142.1, 140.1, 136.1, 135.2, 128.7, 127.3, 121.5, 116.3, 106.4, 75.2, 70.0, 67.0, 56.2, 56.1, 45.7, 43.8, 40.2, 40.0, 36.4, 32.9, 28.7, 27.6, 25.7, 25.6, 23.3, 22.0, 20.2, 18.0, 17.9, 12.1, 7.7, −5.0, −5.09, −5.11. Exact mass for $C_{36}H_{56}OSi$ ($M^+ - H_2O - C_6H_{16}OSi$) requires *m*/*z* 532.4100, found *m*/*z* 532.4103.

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