Chinese Chemical Letters 25 (2014) 771–774

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Improved and efficient synthesis of Maxacalcitol

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ARTICLE INFO

Article history:
Received 18 December 2013
Received in revised form 27 January 2014
Accepted 20 February 2014
Available online 12 March 2014

Keywords:
Vitamin D3 derivative
Maxacalcitol
Synthesis
Asymmetric reduction

ABSTRACT

Maxacalcitol, the 22-oxa-derivative of 1α, 25-dihydroxyvitamin D_3, has been used as an antihyperparathyroidism and antipsoriatic drug. In this paper, an alternative synthetic route has been developed using commercially available vitamin D_2 as the starting material. In addition, as a key intermediate, the asymmetric synthesis of 20(*S*)-alcohol **14** with the chiral auxiliary (*R*-CBS) was described for the first time. This new synthetic route afforded Maxacalcitol with improved overall yield (13.9%) in eleven steps.

1. Introduction

Vitamin D and its analogs constitute a valuable group of compounds that can be used to regulate gene expression in functions as varied as calcium and phosphate homeostasis as well as cell growth regulation and cell differentiation of a variety of cell types, such as keratinocytes, a type of epithelial cell [1]. Several such analogs have been developed as drugs on the market to cure patients suffering from osteoporosis, psoriasis, or renal dysfunction [2]. One of the analogs shown to exert a selective action on the parathyroid glands was 1α,25-dihydroxy-22-oxavitamin D_3 (Maxacalcitol, **1**), which was developed by Chugai pharmaceuticals in Japan and differs from 1,25$(OH)_2$ D_3 only by substitution of an oxygen in place of carbon 22 in the side chain [3]. It has been shown to be highly effective in stimulating monocytic differentiation of human promyelocytic leukemic HL-60 cells. Additionally, the clinical trials indicate that Maxacalcitol not only appears to be safe, suppressing PTH (secondary hyperparathyroidism) and exhibiting positive effects on bone formation, but is also less calcemic than 1,25$(OH)_2$ D_3 [4,5]. The mechanism for the selectivity of Maxacalcitol can be attributed primarily to its low affinity for the serum vitamin D binding protein and altered pharmacokinetics [6]. To date, many methods has been described in the literature to synthesize Maxacalcitol [7–11], especially the strategy as shown in Scheme 1, which was employed by Chugai pharmaceuticals to prepare Maxacalcitol on the industrial scale. Scheme 1 starts with the ketodiol **3**, which was prepared from dehydroepiandrosterone (DEA) **2** *via* microbiological 1α-hydroxylation [7–9]. Unfortunately, all of these processes suffer low yield (no more than 3%), and the starting material ketodiol **3** is monopolized by the company. Many ways for total synthesis of Maxacalcitol are only applicable in the laboratory. Additionally, the byproduct or isomer caused by the co-occurrence of side reactions is difficult to eliminate, leading to tedious work procedures and high production costs. Due to the lack of a more efficient synthetic route, the Maxacalcitol price remains high.

Herein, a novel and highly practical strategy for the synthesis of Maxacalcitol using ergocalciferol (vitamin D_2) as the starting material and other readily available low cost raw materials and reagents has been developed. This method overcomes many weaknesses mentioned in the previous literature. The efficient and versatile synthesis will benefit those people suffering from hyperparathyroidism, dermatologic and psoriasis disease.

2. Experimental

3(*S*)-*tert*-Butyldimethylsilyloxy-9,10-secoergosta-5,7(*E*),10(19),22(*E*)-tetraene (**9**): To a solution of ergocalciferol (200.0 g, 478 mmol) in methylene chloride (1000 mL) under nitrogen, imidazole (7.8 g, 115 mmol) was added followed by TBSCl (8.6 g,

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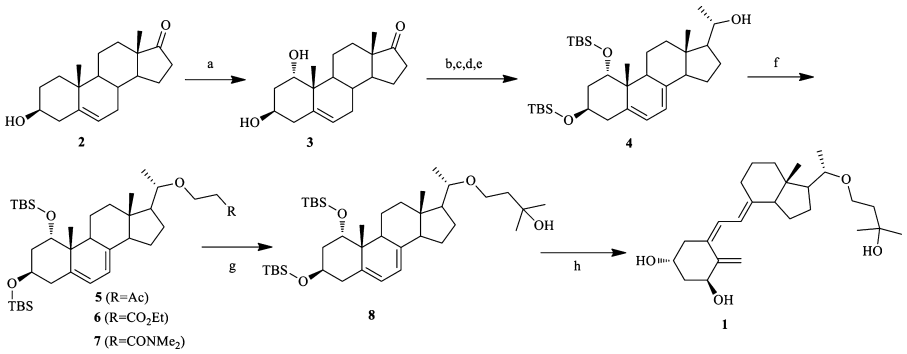
1001-8417/$ – see front matter
http://dx.doi.org/10.1016/j.cclet.2014.03.001



Scheme 1. Chugai Pharmaceuticals reported synthetic scheme of Maxacalcitol. (a) Microbiological 1α-hydroxylation; (b) TBSCl, 50–60 °C; (c) NBS, and then γ-collidine, refluxing; (d) Ph_3PEtBr, *t*-BuOK, r.t.; (e) 9-BBN, H_2O_2/NaOH, r.t.; (f) 4-bromo-1-butene, NaH; and then $PdCl_2$, O_2, r.t. (**5**); ethylacrylate, tetra-*n*-butylammonium hydroxide (**6**); *N*,*N*-dimethylacrylamide, NaH (**7**); (g) MeMgBr/$MeCeCl_2$/MeLi; (h) *hv*, and then heat.

57.4 mmol) at 0 °C, and the mixture was stirred for 4 h at room temperature. The mixture was then treated with water (150 mL), and the organic phase was separated, and the aqueous residue was extracted with methylene chloride (2× 100 mL). The combined solution was added into water (80 mL), and the mixture was used directly in the next step.

SO_2-cycloadduct of 3(*S*)-*tert*-butyldimethylsilyloxy-9,10-secoergosta-5,7(*E*),10(19),22(*E*)-tetraene (**10** or **10′**): To the solution of TBS ether **9**, SO_2 flow was bubbled at room temperature and stirred for 8 h to produce a light green reaction mixture. The remaining sulfur dioxide and the methylene chloride solvent was removed under reduced pressure to afford the Diels–Alder adduct as a crude product. The residue was pumped under high vacuum to further remove SO_2. The oil was taken directly to the next step.

SO_2-cycloadduct of 3(*S*)-*tert*-butyldimethylsilyloxy-20(*S*)-formyl-9,10-secoprega-5,7(*E*),10(19)-triene (**11** or **11′**): To the solution of SO_2 adduct **10** in methylene chloride (600 mL), pyridine (7.8 g, 115 mmol) was added, and O_3 flow was bubbled at −65 °C. The reaction mixture was stirred for 4 h until no more change was detected by TLC. This produced a light green reaction mixture. The reaction mixture was purged with air for 30 min, and the residue was concentrated under reduced pressure to afford **11** or **11′** as an oil crude product. The product was taken directly to the next step.

SO_2-cycloadduct of 3(*S*)-*tert*-butyldimethylsilyloxy-20-one-9,10-secoprega-5,7(*E*),10(19)-triene (**12** or **12′**): **11** (50.7 g, 100 mmol) was stirred into dimethylformamide (500 mL). O_2 was bubbled through the solution, and diazabicyclooctane (DABCO, 11.2 g, 100 mmol) was added, followed by addition of $Cu(OAc)_2$ (3.6 g, 20 mmol) and bipiridyl (3.1 g, 20 mmol). The temperature was kept at a temperature of 35 °C, and the solution was stirred at this temperature for 5 h. The reaction progress was checked by TLC. When the reaction was completed, ethyl acetate and water were added to the mixture. The aqueous phase was washed with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Evaporation under reduced pressure at a temperature of 40 °C gave crude product **12** or **12'** as a brown semi-solid, which was taken directly to the next step.

SO_2-adduct of (3*S*)-*tert*-Butyldimethylsilyloxy-(20*S*)-hydroxy-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (**13** or **13′**): **12** or **12′** (49.2 g, 100 mmol) was dissolved in dry THF (400 mL) and (*R*)-CBS (1 mol/L in THF, 100 mL) was added dropwise slowly at −25 °C, then BH_3 was added dropwise (1 mol/L in THF, 100 mL) at the same temperature. After being stirred for 1 h, saturated aqueous ammonium chloride solution (50 mL) was added, and the mixture was extracted with ethyl acetate. The combined organic phase was dried, filtered, and concentrated in vacuo to give light yellow oil that was used without purification in the next step.

13: $[\alpha]_D^{20}$+58.0 (*c* 1.0, CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ −0.01, −0.00 (d, 6H), 0.52 (s, 3H), 0.82 (s, 9H), 1.18–2.22 (m, 20H), 2.52–2.56 (m, 1H), 3.56–3.68 (m, 3H), 3.91–3.94 (m, 1H), 4.55–4.58 (d, 1H, *J* = 10.4 Hz), 4.73–4.75 (d, 1H, *J* = 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, −4.7, 12.7, 18.1, 22.1, 23.2, 23.7, 24.6, 24.7, 25.8, 29.3, 29.7, 31.0, 34.1, 39.1, 44.6, 55.9, 58.2, 58.5, 66.8, 66.9, 69.9, 110.2, 126.8, 130.3, 149.3; MS (ESI) *m*/*z*: 495 $[M+H]^+$.

13′: $[\alpha]_D^{20}$+7.2 (*c* 1.0, CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ −0.01, −0.00 (d, 6H), 0.60 (s, 3H), 0.82 (s, 9H), 1.17–2.20 (m, 20H), 2.54–2.57 (m, 1H), 3.59 (s, 2H), 3.63–3.68 (m, 1H), 3.93–3.96 (m, 1H), 4.44–4.47 (d, 1H, *J* = 9.2 Hz), 4.64–4.66 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, 12.4, 18.1, 22.0, 23.6, 24.3, 25.0, 25.8, 29.7, 29.7, 30.7, 34.3, 39.3, 45.3, 56.1, 58.1, 58.7, 66.5, 67.6, 70.3, 110.8, 128.5, 130.7, 150.0; MS (ESI) *m*/*z*: 495 $[M+H]^+$.

(3*S*)-*tert*-Butyldimethylsilyloxy-(20*S*)-hydroxy-9,10-secopregna-5,7(*E*),10(19)-triene (**14**): **13** or **13′** was dissolved in ethanol (95%, 400 mL) and $NaHCO_3$ was added. The reaction mixture was warmed to reflux and stirred at this temperature for 3 h. When the reaction was completed, the mixture was filtered though a Buchner funnel and the solvent was evaporated under reduced pressure at 40 °C. The product was purified on a chromatographic column using silica gel with mixtures of ethyl acetate in hexane, to give 35.5 g of **14** as colorless oil (yield 47% in six steps).

14: $[\alpha]_D^{20}$+67.3 (*c* 1.0, CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ −0.01 (d, 6H), 0.50 (s, 3H), 0.82 (s, 9H), 1.16 (d, 3H, *J* = 6 Hz), 1.18–1.23 (m, 2H), 1.35–2.22 (m, 13H), 2.38–2.43 (m, 1H), 2.57–2.61 (m, 1H), 2.79–2.83 (m, 1H), 3.64–3.67 (m, 1H), 3.78–3.81 (m, 1H), 4.58 (s, 1H), 4.86 (s, 1H), 5.81 (d, 1H, *J* = 11.6 Hz), 6.40 (d, 1H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, −4.6, 12.7, 18.2, 22.2, 23.2, 23.6, 25.0, 25.9(3C), 28.8, 31.2, 35.2, 37.5, 39.5, 44.9, 56.3, 58.7, 69.4, 70.3, 107.5, 116.5, 119.9, 136.6, 142.9, 150.0; MS (ESI) *m*/*z*: 431 $[M+H]^+$; HRMS (ESI) *m*/*z* calcd. for $C_{26}H_{42}O_4$: 431.3267 $[M+H]^+$, found: 431.3253.

(3*S*)-*tert*-Butyldimethylsilyloxy-22-oxa-25-hydroxy-9,10-secopregna-5,7(*E*),10(19)-triene (**16**): To the secondary alcohol **14** (43.1 g, 100 mmol) in THF (430 mL), NaH was added (60% dispersion in mineral oil, 6 g, 150 mmol) portionwise with stirring at room temperature for 0.5 h. After the evolution of hydrogen ceased, epoxy bromide (31 g, 200 mmol) was added dropwise at the same temperature with stirring, and the mixture was refluxed for 5 h. After cooling to room temperature, lithium *sec*-butylborohydride (*L*-Selectride, 1 mol/L in THF, 200 mL, 55.06 mmol) was added dropwise, and the mixture was stirred for 3 h. The mixture was then treated with saturated aqueous ammonium chloride solution (100 mL), the organic phase was separated, and the aqueous residue was extracted with ethyl acetate (2× 100 mL). The combined extracts were washed with brine, dried with anhydrous