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Stereoselective synthesis of tacalcitol via (*R*)-MeCBS catalyzed borane reduction

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ABSTRACT

A novel and efficient approach for the synthesis of 1α, 24(*R*)-dihydroxyvitamin D_3 (tacalcitol) starting from readily available enone **1** has been achieved with high stereoselectivity. The key step involved in the synthesis of tacalcitol was the stereoselective reduction of enone **1** using borane as the reducing agent, and the effects of the critical reaction parameters such as temperature, various borane complexes have been examined. Finally, tacalcitol was obtained in five steps from enone **1** with an overall yield of 32% and a ratio of 24-*R*/*S* = 95/5.

1. Introduction

The physiologically active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (calcitriol) has exhibited various pharmacological activities.[1] As a consequence of its classical role in calcium homeostasis and bone mineralization,[2] calcitriol also regulates the proliferation and differentiation of various types of cancer cells[3] and has been used as a potent drug for the treat of proliferative diseases such as psoriasis and leukemia.[4] Inspired by this, the syntheses of vitamin D_3 analogues have been received considerable attention and more than 3000 vitamin D_3 analogues with different structural modifications have been synthesized.[5] Among these analogues, tacalcitol (1α,24(*R*)-dihydroxyvitamin D_3, Fig. 1), which differs structurally from calcitriol by hydroxylation at the 24 position instead of the 25 position displays higher antiproliferative activity and has been already used clinically for the treatment of psoriasis.[6]

To date, many efficient synthesis routes of tacalcitol have been reported. The very first attempt to synthesize tacalcitol using fucosterol as the starting material was reported in 1975, which was obtained through chromatographic separation of a diastereomeric mixture.[7] Fall et al. reported an efficient stereoselective synthesis of tacalcitol through a convergent dienyne approach.[8] Okamoto et al. achieved the total synthesis of tacalcitol via the palladium-catalyzed alkylative enyne cyclization reaction.[9] Matsuo and Ishibashi's group later also accomplished its enantioselective synthesis through asymmetric reduction of 24-oxocholesteryl ester to 24(*R*)-hydroxycholesteryl ester by using borane-diethylaniline as a reducing agent.[10] However, the stereoselective reduction of the prochiral ketone intermediate of tacalcitol is still a difficult problem that remains to be resolved.

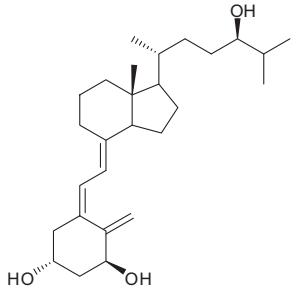

Figure 1. Structure of tacalcitol.

Since our group has successfully synthesized several vitamin D analogues,[11] as a continuation, we herein report an efficient stereoselective synthesis of tacalcitol by (*R*)-MeCBS catalyzed asymmetric reduction[12] of enone **1** with borane as the reducing agent.

2. Results and discussion

2.1. Synthesis of (*R*)-alcohol by stereoselective reduction

The synthesis began from known enone **1**, which was derived from commercially available vitamin D_2 by using our previously reported procedures.[10,11] In order to achieve a concise, flexible approach for the synthesis of (*R*)-alcohol **4**, two different synthetic routes were investigated.

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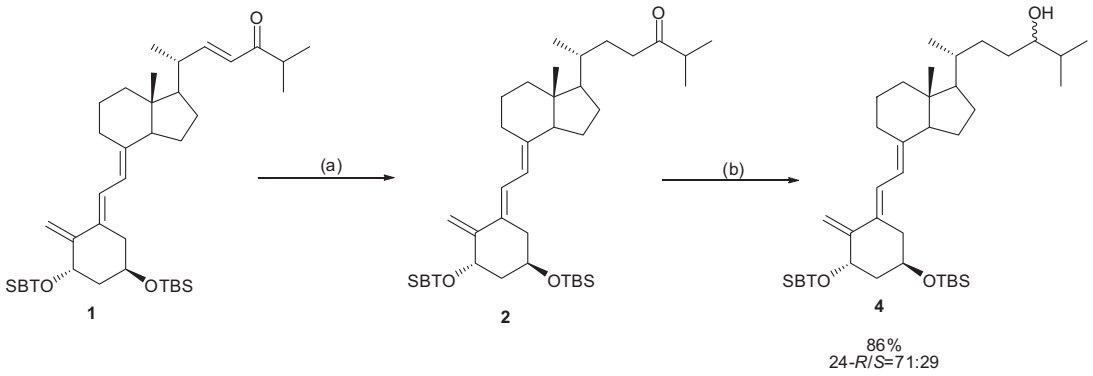

Scheme 1. Synthetic route to the key intermediate **4**. (a) $Na_2S_2O_4$, $NaHCO_3$, $(C_{10}H_{21})_3NMeCl$, $PhCH_3$, H_2O, 80 °C; (b) (*S*)-MeCBS, borane-THF, THF.

Table 1
The reducing agents effect on the enantioselectivity for reduction of ketone **2**

Entry	Alcohol	Catalyst	Reducing agent	Temperature (°C)	Yield (%)	24-*R*/*S*
1	**4**	—	$NaBH_4$	−20	98	53/47
2	**4**	(*S*)-MeCBS	BH_3-THF	−20	86	71/29
3	**4**	(*S*)-MeCBS	BH_3-Me_2S	−20	83	54/46
4	**4**	(*S*)-MeCBS	BH_3-Et_2NPh	−20	94	58/42
5	**4**	(*S*)-MeCBS	Catecholborane	−20	87	66/34

First, enone **1** was reduced with $Na_2S_2O_4$ and $NaHCO_3$ under phase transfer conditions to give prochiral ketone **2** in a yield of 72% (Scheme 1).[10,11] Then the prochiral ketone **2** was reduced to give the (*R*)-alcohol **4** by the (*S*)-MeCBS catalyzed asymmetric reduction using borane as the reducing agent. Prior to the preparation of (*R*)-alcohol **4**, the effect of the critical reaction parameters such as temperature, and various borane complexes have been examined. In an initial study, the influence of various reducing agents, including sodium borohydride, borane-THF, borane-Me_2S, and borane-Et_2NPh was examined on the stereoselectivity of reduction of prochiral ketone **2**. The results are summarized in Table 1. It was found that reduction with BH_3-THF afforded the (*R*)-alcohol with a moderate stereoselectivity (24-*R*/*S* = 71/29, entry 1), while the reaction with borane-Me_2S borane-Et_2NPh and catecholborane provided less stereoselectivity. Since borane complexes not only react with carbonyl, but also react with the conjugated double bonds of the ketone **2**, the results suggest that the reducing agent borane-THF gives the (*R*)-alcohol in a better reaction yield due to minimized side reactions.

To further optimize the reaction conditions of enone **1** reduction, we next examined the effect of temperature on the stereoselectivity and reaction yield. The results are summarized in Table 2. When the temperature was decreased from 20 °C to 0 °C and −20 °C, the product yield of the target compound greatly increased from 0 to 38% and 86%, respectively. However, lowering the reaction temperature did not improve the stereoselectivity and the reaction a required longer reaction time. With the optimized reaction conditions for the borane reduction catalyzed by (*S*)-MeCBS in hand (entry 4), the reaction was finally carried out and the corresponding optically active alcohol **4** was obtained in an excellent yield and a moderate stereoselectivity.

The second synthetic strategy was also attempted as depicted in Scheme 2. Treatment of enone **1** in THF with (*R*)-MeCBS at −20 °C provided compound **3** with an excellent yield of 95% and highly stereoselectivity (24-*R*/*S* = 5:95), because the sizes of the aliphatic vinyl groups on the side chain were more differentiated. Finally the conversion of **3** into the corresponding (*R*)-alcohol **4** was readily achieved in 70% yield under phase transfer conditions.

2.2. Synthesis of tacalcitol by photo-isomerisation and deprotection

In order to synthesize the target compound, (*R*)-alcohol **4** was firstly subjected to photoisomerisation to give **5** using 9-acetylanthracene (9-AA) as sensitizer with the yield of 71% (Scheme 3). Under similar reaction conditions to those described earlier,[10] **5** was then subjected to remove the TBS protecting group using tetrabutylammonium fluoride in THF. When, we tried to remove the TBS protecting group prior to the photo-isomerisation step, we found that the reactant and product were hard to separate. At this point, the former scheme was used to obtain the compound **6**. Finally, tacalcitol was obtained by preparative HPLC using a chiralcel AYH column, ACN 100%, 30 mL/min, retention time = 7.29 min.

Table 2
The temperature effect on the enantioselectivity for reduction of ketone **2**

Entry	Alcohol	Catalyst	Time (min)	Temperature (°C)	Yield (%)	24-*R*/*S*
1	**4**	(*S*)-MeCBS	30	20	—	—
2	**4**	(*S*)-MeCBS	5	20	—	—
3	**4**	(*S*)-MeCBS	30	0	38	70/30
4	**4**	(*S*)-MeCBS	30	−20	86	71/39
5	**4**	(*S*)-MeCBS	90	−40	83	69.5/30.5
6	**4**	(*S*)-MeCBS	180	−40	87	70.5/29.5

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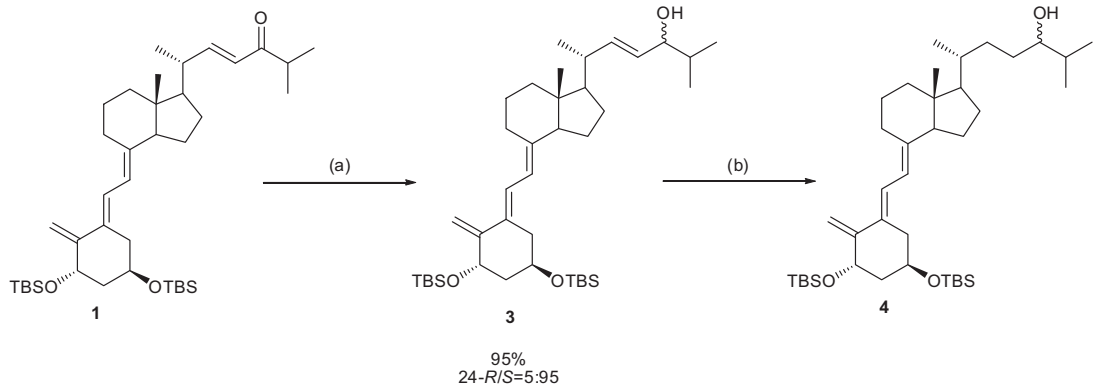
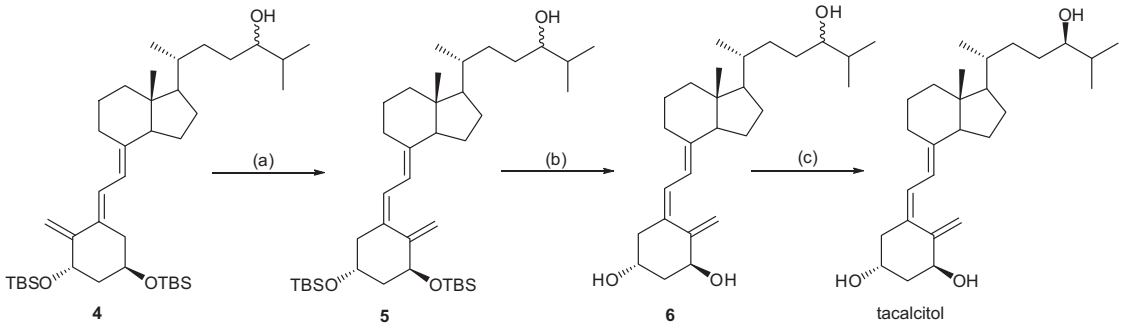


Scheme 2. Synthetic route to the key intermediate **4**. (a) (*R*)-MeCBS, borane-THF, THF; (b) $Na_2S_2O_4$, $NaHCO_3$, $(C_{10}H_{21})_3NMeCl$, $PhCH_3$, H_2O, 80 °C.



Scheme 3. Synthetic route of tacalcitol. (a) 9-AA, hv, toluene, 20 °C; (b) *n*-Bu_4NF, THF, 60 °C; (c) Pre-HPLC.

3. Conclusion

In conclusion, tacalcitol was obtained by using enone **1** as starting material in 32% overall yield in 5 steps, via a novel and concise synthetic route. (*R*)-MeCBS catalyzed asymmetric reduction of enone **1** was the key step. Our synthetic route is a viable route to synthesize tacalcitol.

4. Experimental

4.1. General

All operations were carried out under an atmosphere of ultra-high purity argon in oven-dried glassware. Most of the organic compounds utilized in this study were commercial products of the highest purity. The reactions were monitored by thin-layer chromatography (TLC). ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz with Bruker AvanceIII 500 MHz NMR spectrometer in $CDCl_3$. ^{13}C nuclear magnetic resonance (NMR) were recorded at 125 MHz with Bruker AvanceIII 125 MHz NMR spectrometer in $CDCl_3$. All chromatographic experiments were carried out using a liquid chromatographic system consisting of LC-20AT separation module and ultraviolet detector SPD-20A (all Shimadzu, Japan).

4.2. Synthesis of compound 2

Enone **1** (2.88 g, 4.4 mmol) was added to the stirred mixture of sodium bicarbonate (7.84 g. 45 mmol), sodium hyposulfite (7.56 g, 90 mmol) and methyltridecylammonium chloride (0.7 g) in toluene (100 mL) and water (100 mL) at 80 °C. Upon completion of reaction, extracted with EA (2 × 50 mL), washed with water (2 × 60 mL), brine (2 × 60 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, PE: Et_2O = 100:3, v/v) to yield **2** as a colorless liquid (2.12 g, 73.4%). mp: 76–78 °C; $[\alpha]_D^{20}$ = +38.1 (*c* 0.02, $CDCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (d, 1H, *J* = 11.5 Hz), 5.82 (d, 1H, *J* = 11.5 Hz), 4.98 (s, 1H), 4.94 (s, 1H), 4.54 (m, 1H), 4.22 (m, 1H),1.09 (d, 6H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.86 (s, 9H), 0.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.5, 153.8, 143.4, 135.6, 121.8, 116.6, 106.7, 70.3, 67.3, 56.5, 46.0, 44.0, 41.0, 40.7, 37.4, 36.6, 35.8, 29.9, 29.1, 27.7, 26.0, 25.9, 23.6, 22.4, 18.7, 18.5, 18.4, 18.2, 12.1; HRMS $[M+H]^+$: calcd for $C_{39}H_{70}O_3Si_2$ 642.4863, Found 643.4927.

4.3. Synthesis of compound 4

To a solution of (*S*)-MeCBS (1 M in toluene, 0.2 mL) was added to a solution of borane-THF (2 mol/L) in THF (0.2 mL) under argon atmosphere. The reaction mixture was stirred for 2 h at rt and cooled to −20 °C. To this mixture was added slowly a toluene solution of **2** (128 mg, 0.2 mmol) and stirred for 0.5 h at this temperature. The reaction was showed complete by TLC, then a solution of ammonium chloride in water was added to this mixture, and stirred for additional 30 min. After this, another solution of ammonium chloride in water (30 mL) was poured into this mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), which was in turn washed with saturated brine (2 × 20 mL) and water (2 × 20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and purified by chromatography (SiO_2, PE: EA = 10:1, v/v) to give **4** as a colorless liquid (110 mg, 86%). $[\alpha]_D^{20}$ = −38.6 (*c* 0.02, $CDCl_3$), the ratio of 24-*R*/*S* = 71/29, which was determined by HPLC analysis using a Chiralcel OD column, hexane/*i*PrOH = 95:5, 0.1 mL/min [retention times = 56.4 and 59.9 min for (*R*) and (*S*), respectively]. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 6.46 (d, 1H, J = 11.4 Hz), 5.83 (d, 1H, J = 11.5 Hz), 4.99 (s, 1H), 4.94 (s, 1H), 4.54 (m, 1H), 4.22 (m, 1H), 3.32 (m, 1H), 0.93 (m, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.55 (d, 3H, J = 2.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 142.3, 134.4, 120.8, 115.5, 105.6, 76.4, 76.1, 69.2, 66.3, 55.5, 44.9, 42.9, 39.6, 35.5, 35.7, 32.6, 32.2, 31.2, 31.1, 29.8, 29.6, 27.5, 26.7, 26.6, 24.8, 21.9, 21.2, 17.9, 17.2, 17.1, 16.3, 15.7, 11.1, 5.8.

4.4. Synthesis of compound 3

Similar to the synthesis of **4** from **2**, we obtained the target compound **3** (0.176 g, 0.27 mmol) from **1** (0.191 g, 0.3 mmol) in 95% yield and highly stereoselectivity (24-*R*/*S* = 5/95) as a white solid. mp: 83–86 °C, $[\alpha]_D^{20}$ = −49.2 (*c* 0.02, $CDCl_3$). The ratio was determined by HPLC analysis using a Chiralcel OD column, hexane/*i*PrOH = 95:5, 0.1 mL/min [retention times = 58.4 and 62.2 min for (*R*) and (*S*), respectively], ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, 1H, J = 11.4 Hz), 5.83 (d, 1H, J = 11.5 Hz), 5.51 (dd, 1H, J = 15.5, 8.4 Hz), 5.40 (dd, 1H, J = 15.4, 6.9 Hz), 4.99 (s, 1H), 4.94 (s, 1H), 4.54 (m, 1H), 4.22 (m, 1H), 3.78 (t, 1H, J = 6.4 Hz), 1.07 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 6.7 Hz), 0.92 (s, 9H), 0.90 (d, 3H, J = 7.0 Hz), 0.89 (s, 9H), 0.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 143.0, 139.5, 135.4, 128.7, 121.6, 116.4, 106.6, 78.5, 70.2, 67.2, 56.4, 55.9, 45.8, 43.9, 40.4, 40.3, 36.5, 33.9, 28.9, 28.0, 25.8, 25.7, 23.4, 22.2, 20.6, 18.3, 18.2, 18.1, 18.0, 12.2.

4.5. Synthesis of compound 5

The mixture of alcohol **4** (1.29 g, 2 mmol) and 9-acetylanthracene (222 mg) in toluene (80 mL) was irradiated for 1.5 h by using a 500 W high pressure ultraviolet lamp through a brown uranium quartz filter. The solvent was removed and the residue was purified by column chromatography (SiO_2, PE:EA = 20:1, v/v) to afford 0.92 g (71%) of a white solid. mp: 91–93 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (d, 1H, J = 11.2 Hz), 6.02 (d, 1H, J = 11.3 Hz), 5.18 (s, 1H), 4.87 (s, 1H), 4.37 (m, 1H), 4.19 (m, 1H), 3.32 (m, 1H), 0.92 (m, 9H), 0.88 (s, 18H), 0.54 (s, 3H).

4.6. Synthesis of tacalcitol

To the stirred solution of alcohol **5** (645 mg, 1 mmol) in THF (30 mL) was added 1 M tetrabutylammonium fluoride solution in THF (5 mL, 5 mmol) under Ar. The reaction mixture was then stirred for 3 h at 60 °C. After completion of reaction as monitored by TLC, water (100 mL) was added to the reaction and extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with saturated brine (2 × 20 mL) and water (2 × 20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and purified by chromatography (SiO_2, PE: EA = 1:1, v/v) to give **6** as a white solid (279 mg, 67%). The residue mixture was then separated directly using preparative HPLC (Chiralcel AYH column, ACN100%, 30 mL/min, retention time = 7.29 min) to give the target compound tacalcitol. mp: 99–102 °C, $[\alpha]_D^{20}$ = +49.8 (*c* 0.02, $CDCl_3$) {lit.[9] $[\alpha]_D^{20}$ = +54 (*c* 0.05, EtOH)}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, 1H, J = 11.2 Hz), 6.02 (d, 1H, J = 11.1 Hz), 5.32 (s, 1H), 4.99 (s, 1H), 4.42 (m, 1H), 4.22 (m, 1H), 3.32 (m, 1H), 0.92 (m, 9H), 0.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 143.1, 133.0, 124.9, 117.1, 111.8, 77.4, 70.7, 66.8, 56.3, 45.9, 45.2, 42.8, 40.5, 36.0, 33.6, 33.2, 32.0, 30.6, 29.1, 27.6, 23.6, 22.3, 18.9, 17.2, 16.7, 12.0. MS $[M+H]^+$: calcd for $C_{27}H_{44}O_3$ 416.32, Found 417.20.

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.02.007.

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