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Rapid access to a series of calcitriol analogues with restricted side chain conformation

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ABSTRACT

The synthesis of a series of calcitriol analogues with restricted side chain conformation is described. C-22 modified calcitriol analogues have been prepared from a common intermediate, in which the labile triene system is already present.

Introduction

1α,25-Dihydroxyvitamin D_3 (calcitriol, **1**) (Fig. 1) is the hormonally active form of vitamin D_3 (**2**) and not only regulates calcium homoeostasis, but is also involved in cell differentiation and gene transcription.[1] There has been great interest in the synthesis of calcitriol analogues for specific applications.

For a rational design of the desired analogues, information about the conformation of the hydroxylated side chain in the structure binding to the VDR receptor(s) is needed. The specific interaction of ligands with the ligand-binding domain (LBD) of VDR has focused the attention of the scientific community, since the X-ray crystal structure of deletion mutant VDR complexed with the natural ligand **1** was solved by Moras and co-workers.[2]

Since Okamura and coworkers described the synthesis of calcitriol analogues with an aromatic ring in their side chains,[3a] several other examples of calcitriol analogues with restricted side chain conformation have been described,[3b–h] among them worth mentioning those described by Yamada and co-workers,[4] having C-22 substituted side chain (Fig. 2).

These calcitriol analogues proved to have very interesting biological properties. For example analogue **7** was 100 times more efficient than 1,25-dihydroxyvitamin D_3 (**1**) in cell differentiation, although its affinity for the vitamin D receptor (VDR) was one-seventh of that of **1**. Analogue **5** showed the highest VDR binding activity so far known. Recently, Yamamoto and co-workers[5]

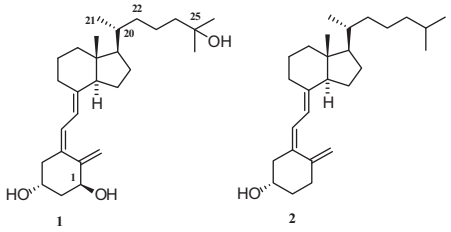

Figure 1. Structures of calcitriol (**1**) and vitamin D_3 (**2**).

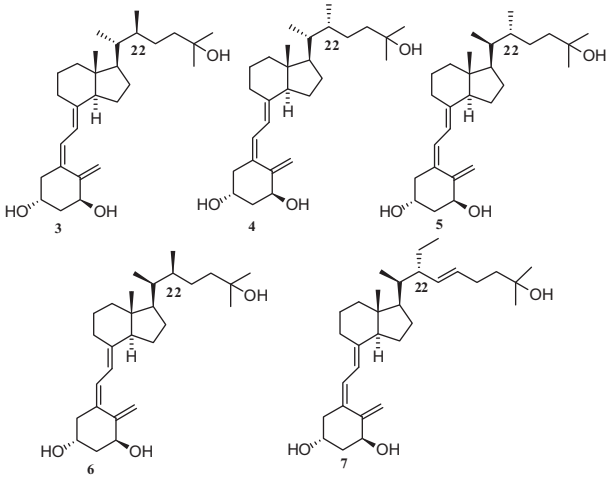

Figure 2. Yamada's type calcitriol analogues.

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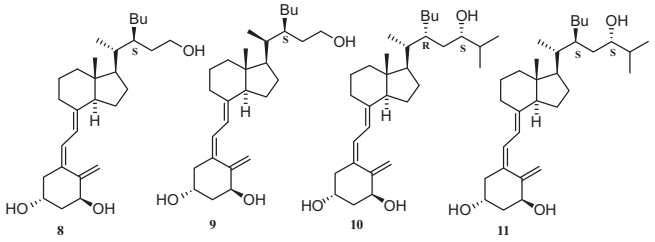


Figure 3. Some of Yamamoto's type calcitriol analogues.

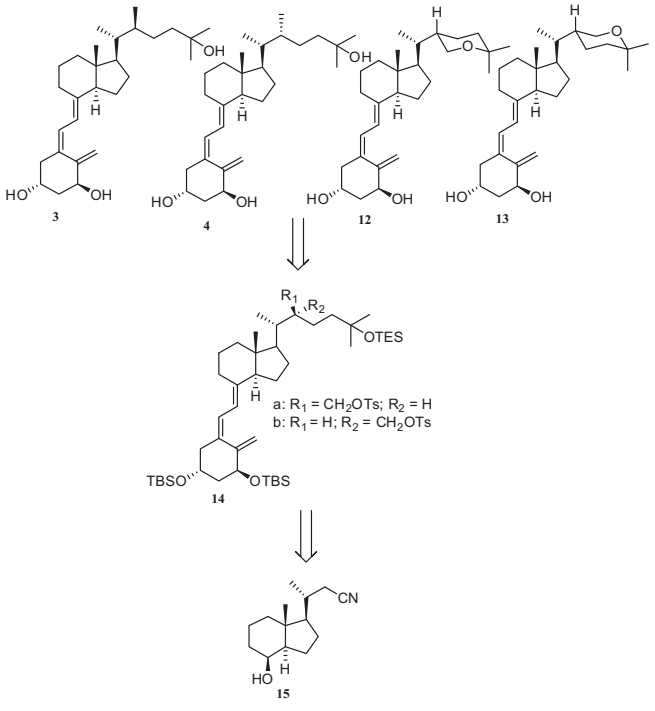
showed that 22-butyl vitamin D derivatives were a new class of vitamin D analogues that induce structural rearrangement of the ligand binding pocket of vitamin D receptor (Fig. 3).

Results and discussion

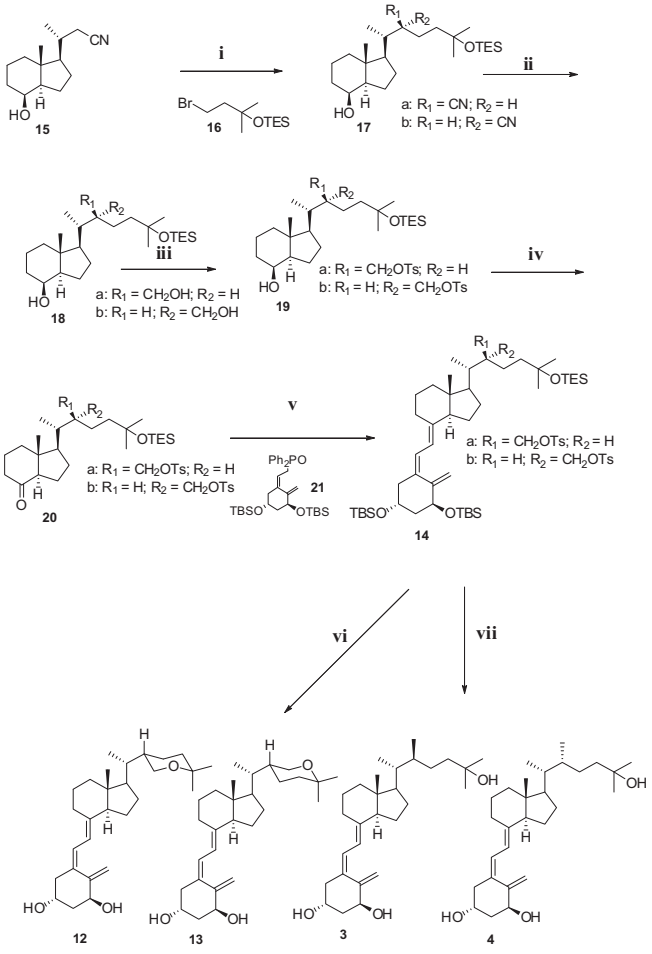
We previously described a synthetic approach to not only Yamada's analogues,[6] but also other new vitamin D analogues with modification at C-22.[7] We now describe a more versatile approach which allows access to a huge series of C-22 modified calcitriol analogues from a common intermediate in which the labile triene system is already present. Our retrosynthetic basis is outlined in Scheme 1.

We anticipated that nitrile **15**,[8] readily available from the Inhoffen-Lythgoe diol could lead to intermediate **14** already bearing the calcitriol triene system. Accordingly target tosylates **14** were prepared as outlined in Scheme 2. Nitrile **15** was uneventfully transformed into known diols **18a** and **18b**[6a] and their primary alcohols were selectively tosylated, affording **19a** and **19b** in 82% and 76% yield, respectively. Pyridinium dichromate oxidation of the alcohols **19a** and **19b** afforded ketones **20a** and **20b** in 91% and 93% yield, respectively. With these key precursors in hand the stage was set for the Wittig–Horner reaction using phosphine oxide **21**.[9] Coupling reaction of **20a** and **20b** with **21** afforded the corresponding targets **14a**[10]and **14b**[11] in 67% and 59% yield, respectively.

Tosylates **14**, on reaction with TBAF afforded known[6a] calcitriol analogues with cyclic side chains **12** and **13** in 69% and 71% yield, respectively. Reaction of tosylates **14** with $LiAlH_4$ followed by



Scheme 1. Retrosynthetic scheme.



Scheme 2. *Reagents and conditions*: (i) LDA, HMPA, THF, −78 °C, **16** (89%); (ii) DIBAH, CH_2Cl_2, −10 °C; HCl; $NaBH_4$, MeOH [**18a** (21%); **18b** (20%); two steps]; (iii) TsCl, Pyr, 0 °C, 12 h [**19a** (82%); **19b** (76%)]; (iv) PDC, CH_2Cl_2, rt, 5 h [**20a** (91%); **20b** (93%)]; (v) **21**; *n*-BuLi, THF, −78 °C [**14a** (67%); **14b** (59%)]; (vi) *n*-Bu_4NF, THF, rt [**12** (69%); **13** (71%)]; (vii) (a) $LiAlH_4$, Et_2O, 0 °C to rt; (b) *n*-Bu_4NF, THF, rt [**3** (33%, two steps); **4** (34%, two steps)].

removal of the silyl protecting groups with TBAF afforded known[6b] target compounds **3** and **4** in 33% and 34% overall yield, respectively.

In conclusion, we have developed a methodology which allows a straightforward synthesis of a large series of calcitriol analogues with restricted side chain conformation which will be used for biological evaluation. This method will allow the study of structure–activity relationship of vitamin D analogues.

Acknowledgments

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10. *Selected data for compound* **14a**: Colourless oil, R_f = 0.75 (30% EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, δ): 7.78 (2H, d, J = 8.28 Hz, H-Ar), 7.33 (2H, d, J = 8.48 Hz, H-Ar), 6.22 (1H, d, J = 11.1 Hz, H-6), 6.00 (1H, d, J = 11.1 Hz, H-7), 5.17 (1H, br s, H-19), 4.86 (1H, br s, H-19), 4.37 (1H, dd, J = 6.5 y J = 3.7 Hz, H-1), 4.19 (1H, q, J = 3.5 Hz, H-3), 4.10 (1H, dd, J = 9.63 y J = 4.5 Hz, H-28), 3.81 (1H, dd, J = 9.6 y J = 4.7 Hz, H-28), 2.81 (1H, d, J = 12.2 Hz. H-14), 2.43 (4H, s, CH_3-Ar y H-9), 2.21 (1H, dd, J = 13.03 y J = 7.25 Hz, H-9), 1.15 (3H, s, H-26 o 27), 1.13 (3H, s, H-26 o 27), 0.91 (9H, t, J = 7.9 Hz, CH_3-TES), 0.87 (18H, s, CH_3-*t*-BuSi), 0.76 (3H, d, J = 6.90 Hz, H-21), 0.52 (9H, m, H-18 y CH_2-TES), 0.06 (6H, s, CH_3-MeSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C-RMN ($CDCl_3$, δ): 148.33 (C-10), 144.51 (C-Ar), 140.50 (C-8), 135.17 (C-5), 133.28 (C-Ar), 129.72 (CH-Ar), 127.89 (CH-Ar), 123 (CH-6), 118.00 (CH-7), 111.07 (CH-19), 73.07 (C-25), 71.95 (CH-3), 71.61 (CH_2-22), 67.47 (CH-1), 56.18 (CH-17), 53.85 (CH-14),45.97 (CH_2), 45.74 (C-13), 44.78 (CH_2), 42.68 (CH_2), 40.50 (CH_2), 40.26 (CH-22), 36.96 (CH-20), 29.96 (CH_3-26 o 27), 29.52 (CH_3-26 o 27), 28.81 (CH_2), 27.52 (CH_2), 25.81 (CH_3-*t*-BuSi), 25.77 (CH_3-*t*-BuSi), 24.40 (CH_2), 23.40 (CH_2), 21.95 (CH_2), 21.56 (CH_3-Ar), 18.18 (C-*t*-BuSi), 18.09 (C-*t*-BuSi), 13.57 (CH_3-21), 11.52 (CH_3-18), 7.06 (CH_3-TES), 6.73 (CH_2-TES), −4.71 (CH_3-MeSi), −4.82 (CH_3-MeSi); MS [m/z, (%)]: 943 [M++1, (11)], 942 [M+, (15)], 812 (25), 811 [M+–OTBS, (28.45)], 810 (52), 638 (34), 266 (26), 257 (34), 249 (24), 248 (100); HRMS: Calcd for $C_{53}H_{94}O_6SSi_3$, 942.6078; found, 942.6034.
11. *Selected data for compound* **14b**: Colourless oil, R_f = 0.69 (30% EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, δ): 7.78 (2H,d, J = 8.27 Hz, H-Ar), 7.33 (2H, d, J = 8.25 Hz, H-Ar), 6.22 (1H, d, J = 11.14 Hz, H-6), 6.01 (1H, d, J = 11.16 Hz, H-7), 5.19 (1H, br s, H-19), 4.86 (1H, br s, H-19), 4.37 (1H, m, H-1), 4.19 (1H, m, H-3), 3.99 (1H, dd, J = 9.85 y J = 4.5 Hz, H-28), 3.85 (1H, t, J = 9.56 Hz, H-28), 2.81 (1H, m, H-14), 2.46 (1H, m, H-9), 2.44 (3H, s, CH_3-Ar), 2.22 (1H, dd, J = 13.1 y J = 7.46 Hz, H-9), 1.16 (3H, s, H-26 ó 27), 1.12 (3H, s, H-26 ó 27), 0.91 (9H, t, J = 7.92 Hz, CH_3-TES), 0.87 (18H, s, CH_3-*t*-BuSi), 0.64 (3H, d, J = 6.69 Hz, H-21), 0.53 (6H, c, J = 7.91 Hz, CH_2-TES), 0.48 (3H; s, H-18), 0.07 (6H, s, CH_3-MeSi), 0.06 (6H, s, CH_3-MeSi); ^{13}C NMR ($CDCl_3$, δ): 148.29 (C-10), 144.53 (C-Ar), 140.64 (C-8), 135.19 (C-5), 133.36 (C-Ar), 129.73 (CH-Ar), 127.90 (CH-Ar), 123.04 (CH-6), 118.00 (CH-7), 111.24 (CH_2-19), 73.06 (C-25), 72.18 (CH_2-22), 72.06 (CH-3), 67.51 (CH-1), 56.34 (CH-17), 53.45 (CH-14), 46.02 (CH_2), 45.71 (C-13), 44.80 (CH_2), 43.69 (CH_2), 40.66 (CH_2), 40.59 (CH-22), 35.48 (CH-20), 30.32 (CH_3-26 o 27), 29.24 (CH_3-26 o 27), 28.86 (CH_2), 27.37 (CH_2), 25.84 (CH_3-*t*-BuSi), 25.81 (CH_3-*t*-BuSi), 23.46 (CH_2), 21.98 (CH_2), 21.59 (CH_3-Ar), 19.05 (CH_2), 18.24 (C-*t*-BuSi), 18.13 (C-*t*-BuSi), 13.04 (CH_3-21), 11.89 (CH_3-18), 7.12 (CH_3-TES), 6.78 (CH_2-TES), −4.60 (CH_3-MeSi), −4.69 (CH_3-MeSi), −4.79 (CH_3-MeSi), −5.08 (CH_3-MeSi); MS [m/z, (%)]: 943 [M++1, (12)], 942 [M+, (21)], 941 [M+–H, (26)], 811 [M+–OTES, (51)], 711 [M+–OTs, (10)], 757 [M+–CH_2OTs, (5)], 678 (9), 638 (44), 507 (16), 355 (11), 257 (39), 248 (100), 173 (41); HRMS: calcd for $C_{53}H_{94}O_6SSi_3$, 942.6078; found, 942.6079.