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Vitamin D heterocyclic analogues. Part 1: A stereoselective route to CD systems with pyrazole rings in their side chains

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Abstract—Efficient preparation of two vitamin D CD ring system synthons with pyrazole rings in their side chains is based on the formation of the pyrazole ring from an α-acetylenic ketone.

1α,25-Dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3[1] (**2**, cholecalciferol), is one of the most potent inducers of calcitropic effects, notably intestinal calcium absorption and bone calcium mobilization. Beside regulating the metabolism of calcium and phosphorus, calcitriol promotes cell differentiation, inhibits the proliferation of tumor cells, and has certain indirect effects on the immunological system.[2] However, the clinical utility of this hormone for treatment of cancers and skin disorders is limited by its hypercalcaemic effects. There is accordingly much interest in the design and synthesis of analogues of **1** with more selective (or even different) biological effects.[2]

In most potentially applicable vitamin D analogues it is the side chain of **1** that is modified (although only a few of the numerous analogues of this type that have been synthesized in recent decades have in fact proved useful for the treatment of cancers[1,2b] or psoriasis[3]). In particular, analogues with rigid, conformationally restricted structural units in the side chain tend to combine non-negligible antiproliferative activity with low calcaemic activity.[4] Inversion of the configuration at C20 can also substantially enhance antiproliferative action.[1] In view of these considerations we propose a synthetic approach to analogue **6** and its C20 epimer **7**, which both include a pyrazole ring in the side chain (Fig. 1). Here we describe the preparation of their CD system and side chain precursors, compounds **4** and **5** (Schemes 1 and 2).

α-Acetylenic ketones having recently been described as highly versatile building blocks for the synthesis of

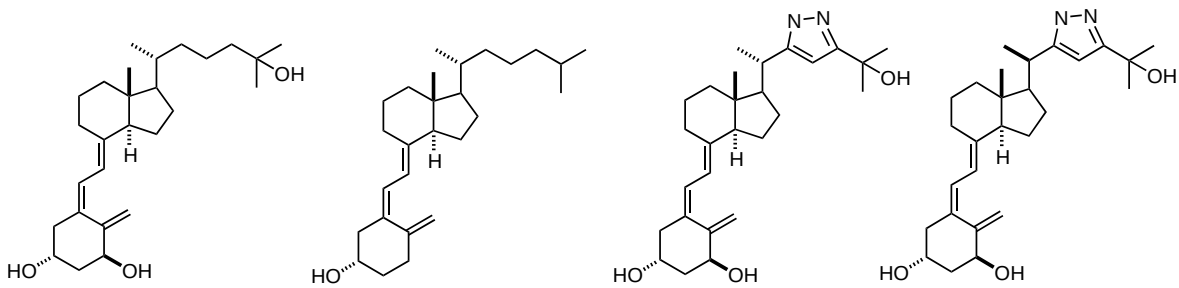

Figure 1.

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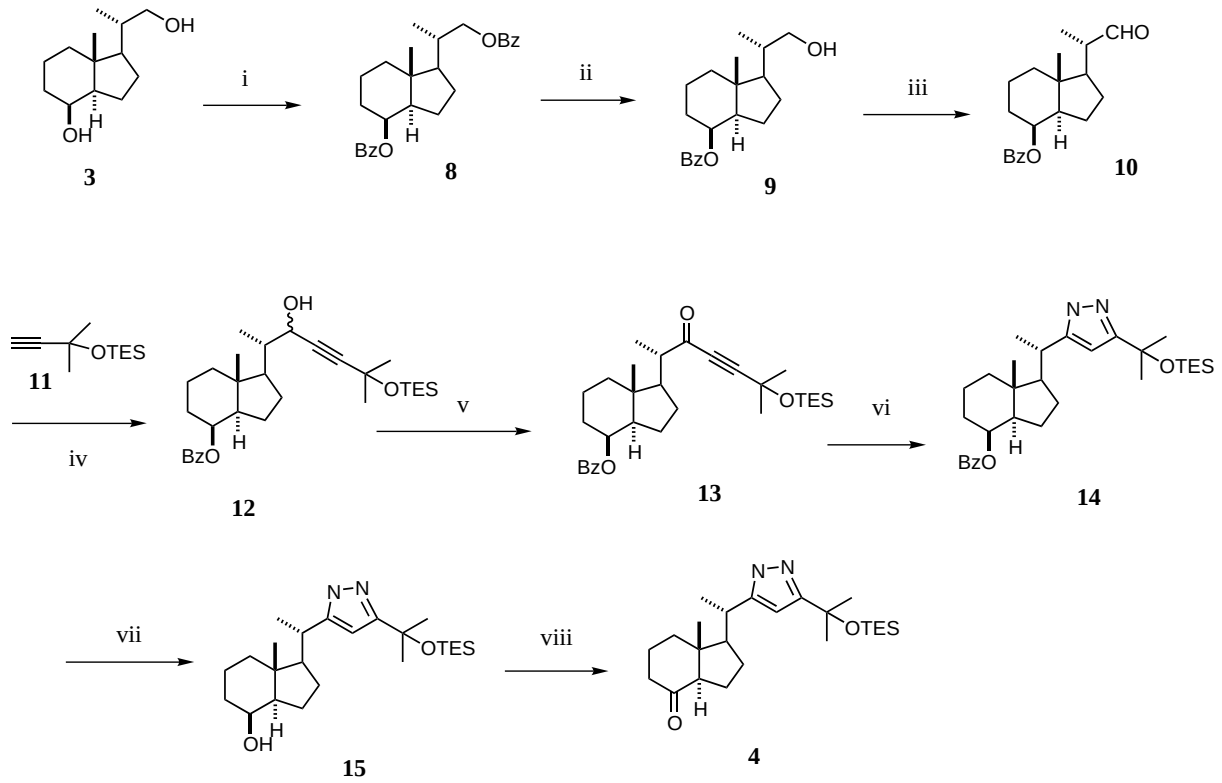
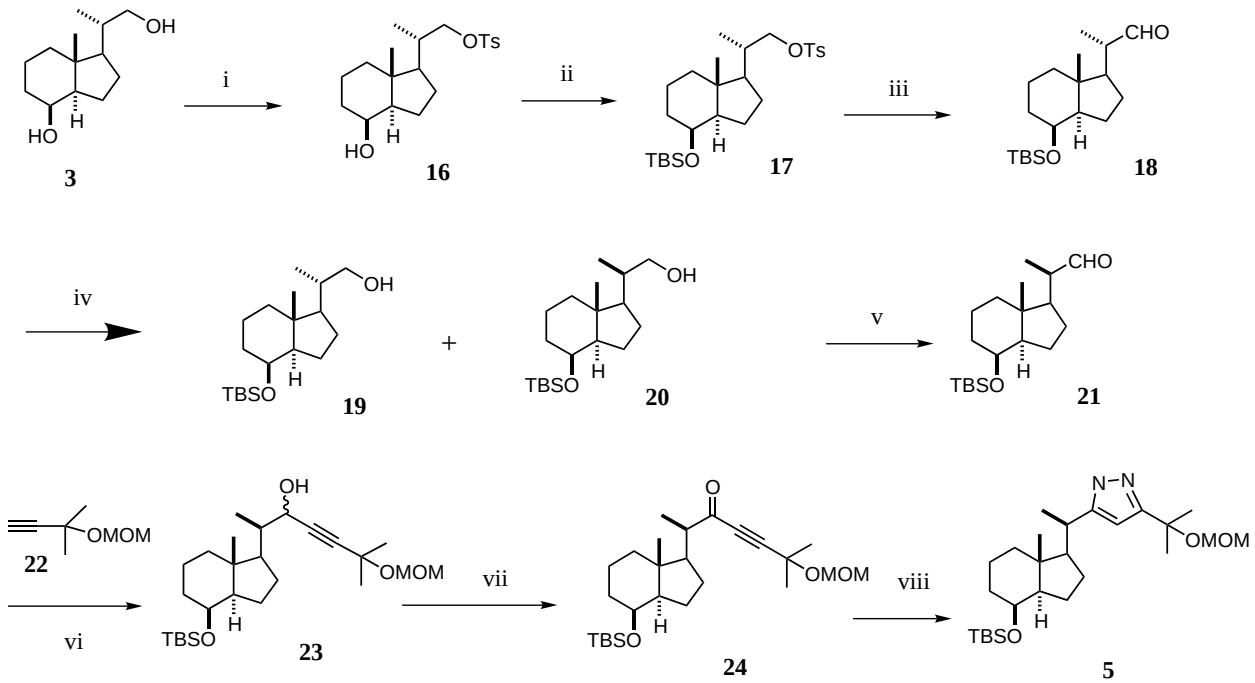


Scheme 1. *Reagents and conditions*: (i) BzCl, py, DMAP, 0°C (99%); (ii) KOH, EtOH, C_6H_6 (95%); (iii) TEMPO, BAIBE, CH_2Cl_2 rt (77%); (iv) **11**, *n*-BuLi, THF, −78°C (78%); (v) PDC, CH_2Cl_2, rt (69%); (vi) NH_2NH_2, DMF, 0°C to rt (95%); (vii) *n*-BuLi, THF (79%); (viii) PDC, CH_2Cl_2, rt, 4 h (83%).



Scheme 2. *Reagents and conditions*: (i) *p*-TsCl, py (93%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10°C (99%); (iii) $NaHCO_3$, DMSO, 120°C (68%); (iv) DBU, THF, 85°C; $NaBH_4$, MeOH, 0°C (75% **19**+**20**); (v) TEMPO/BAIBE, CH_2Cl_2, rt (75%); (vi) **22**, *n*BuLi, THF, −78°C (70%); (vii) PDC, CH_2Cl_2, rt (63%); (viii) NH_2NH_2, DMF, 0°C to rt (84%).

heterocyclic systems,[9] we decided to construct the side chain of **4** via the α-acetylenic ketone **13**. The Inhoffen–Lythgoe diol (**3**), which is readily obtained by degradation of vitamin D_2,[5] was converted to dibenzoate **8** in almost quantitative yield (99%); selective reduction of the primary benzoate of **8** afforded alcohol **9** in 95% yield;[6] oxidation of **9** using 2,2,6,6-tetramethylpiperidine-1-oxyl and [bis(acetoxy)yodo]benzene (TEMPO/BAIBE) gave aldehyde **10** in 77% yield; **10** reacted with the anion obtained by treatment of **11**[7] with *n*-butyllithium, affording propargyl alcohol **12**[8] (78%); and PDC oxidation of **12** afforded the desired α-acetylenic ketone **13**[8] (69%). Gratifyingly, reaction of **13** with aqueous hydrazine afforded **14**,[8] which bears the desired side chain, in excellent yield (95%) and without any epimerization at C20. Removal of the benzoyl group of **14** with *n*-BuLi (79%), followed by PDC oxidation of the resulting alcohol (**15**),[8] gave the target CD synthon **4**[10a] in 83% yield.

For the synthesis of **5** we designed a slightly different route (Scheme 2).

Selective tosylation of the primary alcohol of diol **3** gave tosylate **16** in 93% yield, and protection of the secondary alcohol of **16** (99%), followed by a Kornblum reaction, afforded a 68% yield of aldehyde **18**,[11] from which a mixture of epimeric aldehydes was obtained by equilibration under basic conditions. Reduction of this mixture with $NaBH_4$ gave the corresponding C20- epimeric alcohols **19** and **20**,[12] chromatographic separation of which afforded the desired alcohol **20** in 44% yield (epimer **19** was obtained in 31% yield). Oxidation of **20** gave aldehyde **21**[8] in 75% yield, reaction of the latter with the anion obtained by treatment of **22**[7] with *n*-butyllithium afforded propargyl alcohol **23**[8] in 70% yield, and PDC oxidation of **23** gave α-acetylenic ketone **24**[8] (63%). As hoped, reaction of **24** with aqueous hydrazine afforded a good yield (84%) of compound **5**,[10b] which bears the desired side chain.

The synthesis of analogues **6** and **7**, and of a series of derivatives with substituents on the pyrazole ring,[13] is currently under way in our laboratory with a view to their biological evaluation.

Acknowledgements

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10. (a) Compound **4**: ^1H NMR (300 MHz, $CDCl_3$), δ: 5.8 (1H, s), 2.75 (1H, m), 2.47 (1H, dd, $J=11.4$, 7.1), 1.55 (6H, s, CH_3-26 and CH_3-27), 1.27 (3H, d, $J=6.9$, CH_3-21), 0.90 (9H, t, $J=7.9$, $SiCH_2\underline{CH_3}$), 0.70 (3H, s, CH_3-18), 0.53 (6H, q, $J=7.9$, $Si\underline{CH_2}CH_3$); ^{13}C NMR ($CDCl_3$), δ: 211.75 (C=O), 156.63 (C), 153.58 (C), 97.96 (C=), 71.24 (C-25), 61.89, 56.70, 49.71 (C-13), 40.89 (CH_2), 38.86 (CH_2), 35.76, 31.56, 27.82 (CH_2), 24.01 (CH_2), 21.16, 18.94 (CH_2), 12.38, 6.92, 6.32 (CH_2). HRMS calcd for $C_{24}H_{42}N_2O_2Si$: 419.3049; found: 419.3078; (b) Compound **5**: white solid, mp 119–120°C. ^1H NMR (300 MHz, $CDCl_3$), δ: 5.93 (1H, s), 4.55 (2H, s, OCH_2O), 3.97 (1H, br s, CH-8), 3.31 (3H, s, OCH_3), 2.72 (1H, dd, $J=10.5$, 6.9), 1.97 (1H, d, $J=12.3$), 1.80 (1H, m), 1.65 (1H, m), 1.59 (6H, s, CH_3-26 and CH_3-27), 1.22 (3H, d, $J=6.9$, CH_3-21), 0.97 (3H, s, CH_3-18), 0.86 (9H, s, *t*-BuSi), −0.02 (3H, s, MeSi), −0.04 (3H, s, MeSi); ^{13}C NMR ($CDCl_3$), δ: 154.18 (C), 153.55 (C), 99.94 (CH=), 92.18 (CH_2), 74.18 (C), 69.35, 56.92, 55.32, 53.03, 42.19, 40.66 (CH_2), 35.00 (C), 34.39 (CH_2), 28.04, 27.81 (CH_2), 265.79, 22.89 (CH_2), 20.94, 18.00, 17.65 (CH_2), 11.63, −4.81 ($SiCH_3$), −5.18 ($SiCH_3$). LRMS; *m*/*z* (I, %): 464 (M^+, 3), 404 (64), 377 (28), 345 (100), 271 (19), 135 (25). HRMS calcd for $C_{26}H_{48}N_2O_3Si$: 464.3434; found: 464.3422. Anal. calcd for $C_{26}H_{48}N_2O_3Si$: C, 67.19; H, 10.41; N, 6.03; found: C, 66.92; H, 10.50; N, 6.33.

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