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Synthesis of vitamin D analogues with a 2-hydroxy-3-deoxy ring A†

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Abstract

We present a short, practical synthesis of new C2-hydroxylated vitamin D analogues. The enantioselective synthesis of a phosphine oxide precursor involves, as key step, a catalytic asymmetric allylation.
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Keywords: vitamin D; asymmetric allylation.

Specific vitamin D receptors have been found in more than 30 tissues, and the biological functions of 1α,25-dihydroxyvitamin D_3 (**2a**), the hormonally active form of vitamin D_3 (**1**), are now thought to include promotion of cell differentiation, inhibition of tumor cell proliferation, and induction of functions related to the immunological system.[1] This has prompted significant efforts to design and synthesize analogues that can selectively trigger one or more of the various biological responses of this hormone.[2] In particular, it has been reported that analogues with an additional substituent at position C2 stimulate differentiation in HL-60 cells while having little bone calcium mobilization capacity.[3] Analogues of this type, such as **2b**, offer promise for the treatment of osteoporosis.[4] We wondered whether such biological activity may be promoted by analogues containing a single hydroxyl group at C2. As a step towards answering this question, we have obtained the new vitamin D analogues **3a** and **3b**, which bear a hydroxyl group at C2,[5] by Wittig–Horner coupling between the known ketone **5**[6] and the anion of phosphine oxide **4** (Scheme 1), which was prepared from 4-pentyn-1-ol (Scheme 2).[7] In future work we aim to link the A ring of **4** to a variety of different upper moieties.

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† This paper is dedicated to Professor José Barluenga in honor of his 60th birthday.
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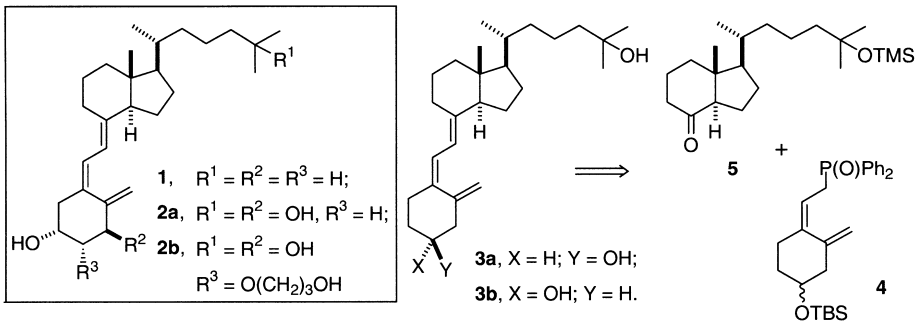
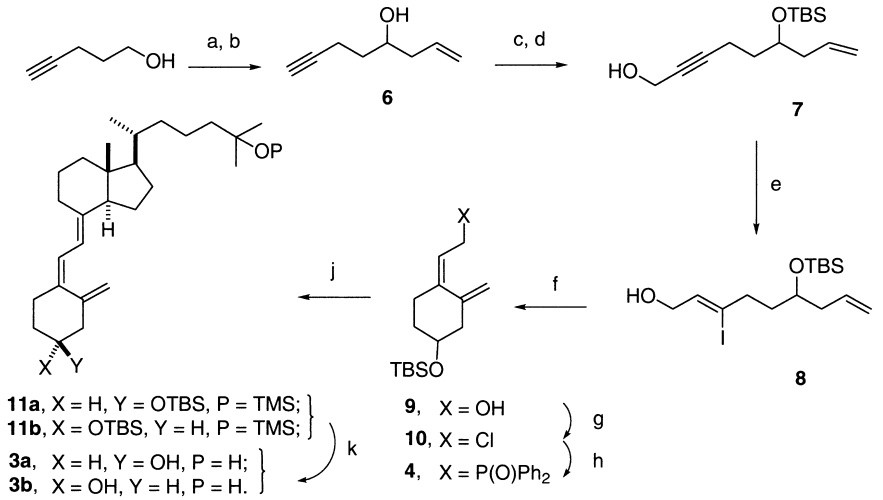


Scheme 1.



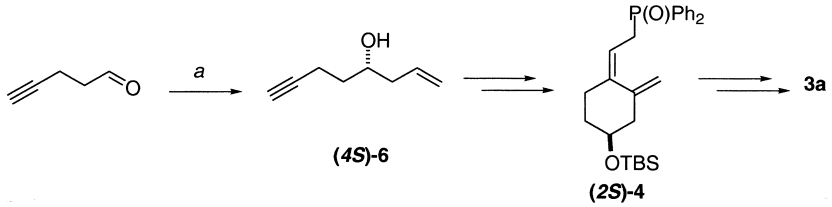
Scheme 2. (a) ClCOCOCl, Et_3N, DMSO; (b) $CH_2{=}CHCH_2MgBr$, THF, 70% (two steps); (c) TBSCl, Im, DMF, 92%; (d) *n*-BuLi, $(CH_2O)_3$, 91%; (e) Red-Al, I_2, THF, 70%; (f) $(Ph_3P)_4Pd$, Et_3N, CH_3CN, reflux, 85%; (g) NCS, Me_2S; (h) (i) Ph_2PH, *n*-BuLi, THF; (ii) H_2O_2, 50% (three steps); (j) *n*-BuLi, THF and then **5**, 65%; (k) TBAF, THF, 95%

Swern oxidation of 4-pentyn-1-ol, followed by addition of allylmagnesium bromide, afforded alcohol **6** in 70% (two steps).[8] Silylation of **6** and subsequent metallation with butyllithium, followed by reaction of the resulting lithium derivative with *p*-formaldehyde, afforded propargyl alcohol **7** (91%). Successive treatment of **7** with sodium bis(2-methoxyethoxy)aluminium hydride and freshly sublimed iodine produced the *Z*-vinyl iodide **8** (70%), which was subjected to intramolecular Heck cyclization[9] with $(Ph_3P)_4Pd/Et_3N$ in refluxing acetonitrile, to affording **9** (85%) as the only detectable product. Finally, alcohol **9** was converted to phosphine oxide **4** by successive reaction with *N*-chlorosuccinimide, lithium diphenylphosphine and H_2O_2.

The vitamin D triene system was constructed by a Wittig–Horner reaction[10] between ketone **5** and the anion derived from **4**, which gave a 1:1 mixture of protected vitamin D analogues **11a** and **11b**. Interestingly, these diastereoisomers were easily separated by flash chromatography to give, after deprotection by treatment with tetrabutylammonium fluoride, **3a** and **3b**.

The configuration of these vitamin D analogues at C2 was confirmed by using enantiomerically pure phosphine oxide **4** in the synthesis of **3a**. As a key step towards the 2*S* enantiomer of **4**,[11] we

performed an asymmetric allylation of 4-pentynal (Scheme 3).[12] Although synthesis of the 2*R* enantiomer of **6** using equimolecular amounts of allylborane prepared from (–)-β-methoxydiisopinylcampheylborane has recently been described,[13] we preferred to evaluate a catalytic strategy. Treatment of 4-pentynal with a 150 mol% excess of allyltrimethylsilane in the presence of 10 mol% of (*R*)-BINOL and TiF_4,[14] gave alcohol (4*S*)-1-octen-7-yn-4-ol [**(4*S*)-6**] in 62% yield and 70% ee.[15] Higher yield (80%) and enantiomeric excess (97%) were obtained when the reaction was carried out at 0°C with allyltributylstannane and 10 mol% of catalyst prepared by heating a 2:1 mixture of (*R*)-BINOL and $Ti(O\text{-}i\text{-}Pr)_4$.[16] Alcohol **(4*S*)-6** was transformed into the 2*S* enantiomer of **4** in 36% yield by the above four-step procedure, and Wittig–Horner reaction of **(2*S*)-4** with ketone **5**, followed by desilylation (TBAF), afforded a compound with ^1H and ^{13}C NMR spectra identical to those of **3a**.



Scheme 3. (a) $CH_2{=}CHCH_2SnBu_3$, (*R*)-BINOL, $Ti(O\text{-}i\text{-}Pr)_4$, THF, 80%, 97% ee

To sum up, we have synthesized a vitamin D ring A analogue with a single hydroxyl group at C2 in good chemical yield and high enantiomeric excess. This ring A can be linked to a variety of upper moiety analogues. Biological assays of analogues **3a** and **3b** are underway.

Acknowledgements

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8. All compounds showed satisfactory analytical and spectroscopic data. Compound **(2*S*)-4**:[11] $[\alpha]_D = +5.55$ (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.7–7.4 (10H, m, Ar), 5.35 (1H, q, $J = 8.4$ Hz, H-6), 4.91 (1H, s, H-19E), 4.73 (1H, s, H-19E), 3.75 (1H, m, H-2), 3.29 (1H, m, H-7), 0.89 (9H, s, *t*-BuSi), 0.08 (6H, s, Me_2Si); ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ: 145.1, (d, $J_{P-C} = 10.2$ Hz), 143.4, 133.8 (d, $J_{P-C} = 36.4$ Hz), 132.5 (d, $J_{P-C} = 36$ Hz), 132.2, 131.5 (d, $J_{P-C} = 7.6$ Hz), 131.3 (d, $J_{P-C} = 7.8$ Hz), 128.9 (d, $J_{P-C} = 9.7$ Hz), 113.4, 111.9 (d, $J_{P-C} = 7.1$ Hz), 70.6, 45.8, 36.2, 33.8, 31.3 (d, $J_{P-C} = 62.8$ Hz), 26.2, 18.5, –4.3. Compound **3a**: ^1H NMR (CD_2Cl_2, 250 MHz) δ: 6.20, 5.99 (2H, AB, $J = 11.2$ Hz, H-6 y H-7), 5.05 (1H, br s, H-19E), 4.84 (1H, br s, H-19Z), 3.85 (1H, m, H-2), 2.81 (1H, m, H-14), 1.15 (6H, s, Me-26 and Me-27), 0.92 (3H, d, $J = 6.5$ Hz, Me-21), 0.52 (3H, s, Me-18); ^{13}C NMR (CD_2Cl_2, 62.83 MHz) δ: 143.7, 142.6, 138.7, 121.0, 118.4, 114.9, 71.5, 70.3, 57.4, 57.1, 46.6, 45.6, 45.2, 41.4, 37.3, 37.0, 36.0, 33.9, 29.9, 29.8, 29.7, 28.4, 24.4, 23.0, 21.6, 19.4, 12.5. Compound **3b**: ^1H NMR (CD_2Cl_2, 250 MHz) δ: 6.19, 6.00 (2H, AB, $J = 11.2$ Hz, H-6 y H-7), 5.05 (1H, br s, H-19E), 4.84 (1H, br s, H-19Z), 3.81 (1H, m, H-2), 2.80 (1H, m, H-14), 1.15 (6H, s, Me-26 and Me-27), 0.92 (3H, d, $J = 6.5$ Hz, Me-21), 0.52 (3H, s, Me-18); ^{13}C NMR (CD_2Cl_2, 62.83 MHz) δ: 144.7, 143.6, 139.7, 122.0, 119.5, 115.8, 72.5, 71.6, 58.5, 58.2, 47.7, 46.9, 46.3, 42.4, 38.3, 38.0, 37.3, 35.3, 31.0, 30.9, 30.8, 29.5, 25.5, 24.2, 22.7, 20.5, 13.5.
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