A Radical Cyclization Approach to 1α,25-Dihydroxyvitamin D_3

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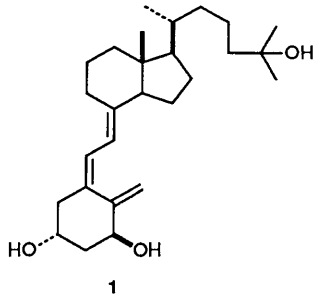
An approach to 1α,25-dihydroxyvitamin D_3 involving the preparation of the vinyl selenide **8**, its cyclization to **9** with tributyltin hydride and the conversion of the latter into the known isomeric dienes **3** and **10** is described.

The recently discovered involvement of 1α,25-dihydroxyvitamin D_3 (calcitriol) **1** in the regulation of cell differentiation and proliferation [1] in addition to its more established role in calcium homostasis has given new impetus to the synthesis of this highly functionalised seco-steroid.[2] We describe here the extension of our recently described radical cyclization methodology for the synthesis of the calcitriol A-ring model **2** [3] to the widely applied synthon **3**.[4]



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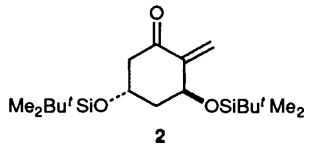

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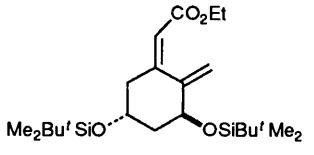
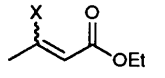


3

The initial reaction scheme, which called for the synthesis of **3** from **2** by Wittig, Horner–Emmons or Peterson type chemistry, proved unworkable owing to the ease of elimination of the *tert*-butyldimethylsiloxy group from C-5 followed by aromatisation. Consequently we turned our attention to the incorporation of the two carbon side chain before cyclization. Hence the heptenoic acid **4**,‡ prepared analogously to **5** used in our previous work,[3],§ was treated with carbonyl diimidazolide (CDI) followed by monoethyl malonate and magnesium ethoxide under the Masamune conditions [5] to give the β-ketoester **6** in 81% yield. Treatment of this β-ketoester with diphenyl chlorophosphate under phase transfer conditions [6] gave the vinyl phosphate **7** in 98% yield as a 10:1 *E*/*Z* mixture. Displacement of the phosphate moiety in **7** was achieved by stirring in tetrahydrofuran (THF) with sodium phenylselenide, generated ultrasonically from diphenyl diselenide and sodium dispersion,[7] giving the vinylselenide **8** in 29% yield as a 1:1 *E*/*Z* mixture and the ketoester **6** in 64% yield. The formation of **6** in this last step is the result of severe steric hindrance around C-3 in **7** leading to effective competing attack by the nucleophile at the phosphorus centre (in a model system the vinyl phosphate **11** gave the selenide **12** in excellent yield). All attempts to circumvent this problem have so far failed. Fortunately the reaction is clean and the ketoester **6** is readily recycled enabling the preparation of respectable amounts of the radical precursor **7**. Heating **8** to reflux in benzene followed by the addition of tributyltin hydride and azoisobutyronitrile (AIBN) as initiator gave a 1:1:2:1 mixture of the four isomers of **9**, separable by silica gel chromatography, in a combined yield of 67%. Finally each of the separate isomers of **9** were converted to the target compound **3** or its *E*-isomer **10**, whose photostimulated equilibration in favour of **3** is an established process,[4] in yields ranging from 60–80% by controlled oxidation with magnesium monoperoxyphthalate (MMPP) and *syn*-elimination of the resultant sulphoxides in toluene at reflux (Scheme 1).



11 X = OP(O)(OPh)$_2$
12 X = SePh

Experimental

Preparation of Vinylselenide **8**.—To a solution of the unsaturated phosphate **7** (200 mg, 0.24 mmol) stirring in THF (5 cm^3) under nitrogen, was added a suspension of sodium phenylselenide (2.4 mol dm^{-3}; 0.13 cm^3, 0.30 mmol) during 5 min. Stirring was continued until all the starting material had been consumed (*ca.* 1.5 h) and the resultant yellow solution was poured into a mixture of ether (10 cm^3) and water (10 cm^3). The aqueous phase was separated and extracted further with ether (2 × 5 cm^3) and the combined ether layers were washed with saturated brine (5 cm^3) before drying ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure yielded a yellow oil. Purification by silica gel column chromatography (eluent, light petroleum–ether, 25:1) afforded the unsaturated phenylselenide **8** as a 1:1 mixture of *E* and *Z* isomers (51 mg, 29%) and recovered **6** (57 mg, 64%).

Preparation of Compound **9**.—To a refluxing solution of the *E* and *Z* unsaturated phenylselenides **8** (150 mg, 0.20 mmol) in dry benzene (10 cm^3) under nitrogen, was added a solution of tributyltin hydride (65 mg, 0.22 mmol) in benzene (1.0 cm^3) with a trace of AIBN, dropwise during 20 min. The reaction was refluxed for a further 5 h, with periodic addition of AIBN, before being cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, light petroleum–ether, 30:1) to yield the 4 diastereoisomers **8** in a 1:1:2:1 ratio (79 mg, 67%).

Preparation of Compounds **3** *and* **10**.—To a stirring solution of **9** (0.05 mmol) in ethanol (2.0 cm^3) under nitrogen at room temperature was added a solution of MMPP (80%; 16 mg, 0.02 mmol) in water (0.5 cm^3). Stirring was continued for 1 h before the mixture was poured into chloroform (10 cm^3), washed with

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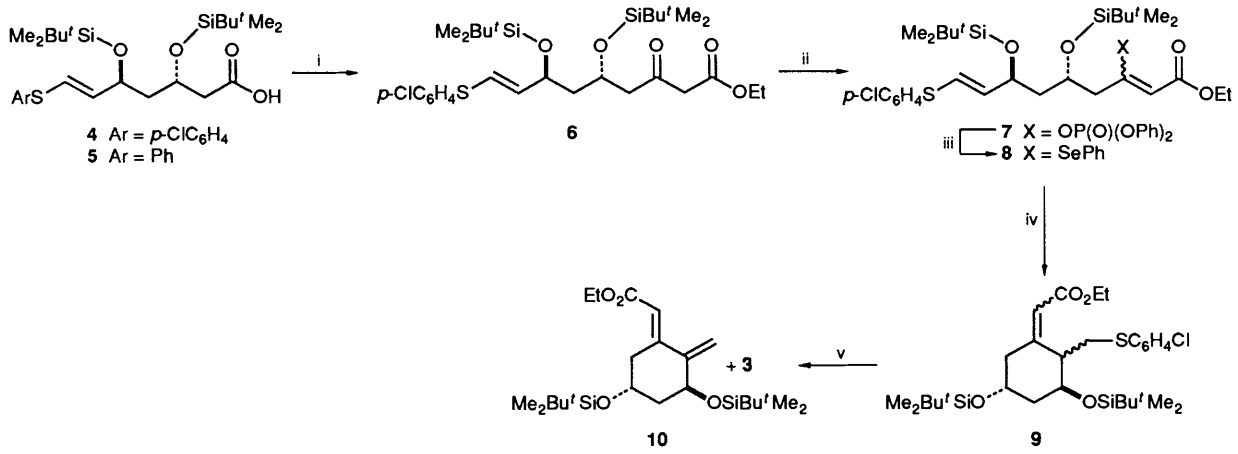
‡ All compounds are racemic; all new compounds gave spectroscopic and microanalytical and/or high resolution mass spectral data in accordance with the assigned structures.
§ We have replaced the phenylthio moiety used in the preparation of **5** by the 4-chlorophenylthio in that of **4** for the simple reason that several of the intermediates can be crystallised and so more readily purified.



Scheme 1 *Reagents and conditions:* i, CDI, $EtOOCCH_2CO_2H$, $(EtO)_2Mg$; ii, $(PhO)_2POCl$, NaOH, CH_2Cl_2, Bu_4NHSO_4; iii, PhSeNa; iv, Bu_3SnH, AIBN; v, MMPP, 110 °C

aqueous sodium hydrogen carbonate (5%; 2 × 5 cm^3) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded the crude sulphoxides as a colourless oil. The sulphoxides were dissolved in toluene (0.2 cm^3) and added dropwise to refluxing toluene (5 cm^3) under nitrogen. Reflux was continued for 2.5 h, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Preparative TLC on silica (eluent, light petroleum–ether, 20:1) afforded either **3** or **10** depending on the starting stereoisomer of **9** (60–80%).

Acknowledgements

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References

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