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A Chemoenzymatic Synthesis of A-ring Key-intermediates for 1α,25-dihydroxyvitamin D_3 and Analogues

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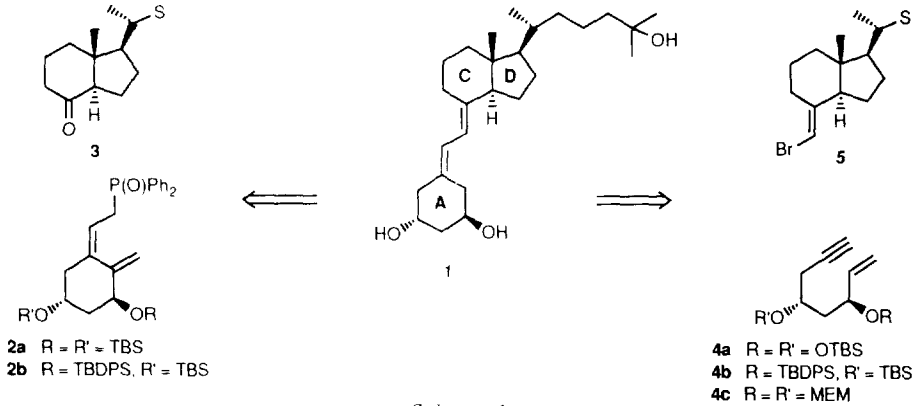
Abstract *: A short and practical synthesis of the 1,7-enyne A-ring intermediate and of Uskokovic's phosphine-oxide precursor is described starting from the aldol product of acrolein with t-butyl acetate. Enantiopure β-hydroxy ester is obtained upon lipase-catalyzed resolution.*

It is presently well established that the hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (**1**; 1α,25$(OH)_2D_3$) may generate biological responses via regulation of gene transcription.[1] The discovery of the presence of specific vitamin D receptors in more than 30 tissues initiated consideration of possible functions of 1α,25$(OH)_2D_3$ (**1**) outside its classical role in calcium-bone homeostasis. The hormone was found to be capable of regulating cell proliferation and differentiation of a variety of immunological and malignant cells. In view of this extraordinary flexibility, current research is aimed at the synthesis of analogues with superagonistic potency and especially with dissociation of effects on cell differentiation compared with their calcemic effects.[1,2]

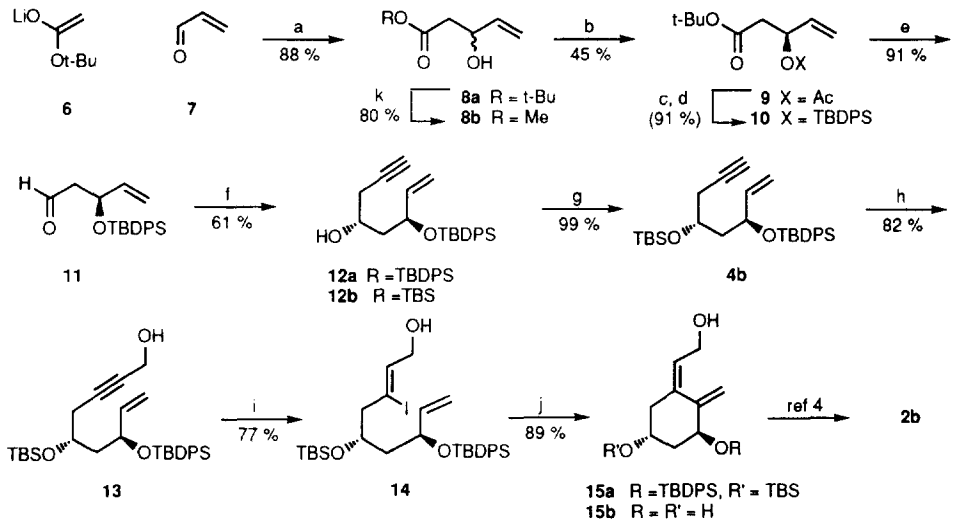
A convergent modular synthesis of analogues, modified in the C/D ring or side chain (S) fragments, involves coupling of an A-ring precursor with a suitable C/D-S moiety (Scheme 1). An effective method is based on Lythgoe's classical synthesis[3] of vitamin D consisting of reaction of the anion of **2a** with Windaus-Grundman ketone derivatives (**3**). Since Uskokovic's[4] synthesis, a number of other approaches of phosphine oxide **3** have emerged.[5]



Scheme 1

Recently a conceptually new construction of the vitamin D skeleton has been developed by Trost *et al.*[6] and involves Pd-catalyzed alkylative enyne cyclization of the 1,7-enyne **4a** and the vinyl bromide **5**. Trost *et al.*[7] has reported an 8-step synthesis of **4a** (96 % ee, 78 % de) while recently Moriarty *et al.*[8] described a diastereoselective synthesis of **4c** from D-xylose in 13 steps.

We want to report an alternative short and practical route to A-ring precursor **4b** and subsequently to **2b**. The construction of the enantiopure 3S,5R-oct-1-en-7-yne-3,5-diol derivative **4b** starts with the aldol reaction of acrolein (**7**) with the lithium enolate of t-butyl acetate (**6**). Kinetic resolution of the resulting racemic β-hydroxy ester **8a** could be performed *via* lipase-catalyzed esterification with vinyl acetate. PS-Amano lipase was found to be highly efficient and gave the desired S-acetate **9**[9] in >99 % ee and 45 % yield.[10] The enantiomeric excess was determined by capillary GC on derivatized cyclodextrines.[11] (Scheme 2)



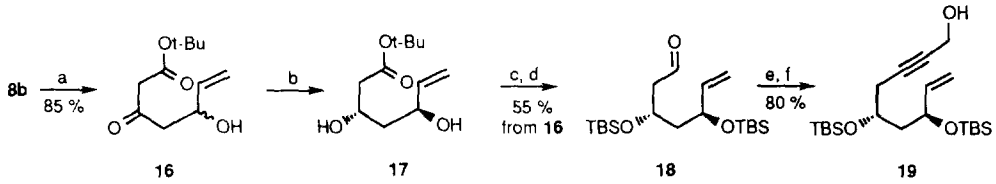
(a) THF, -78°C, 5 min; (b) lipase PS Amano, vinyl acetate, pentane, 30°C, 45 h; (c) K_2CO_3, MeOH, r.t., 1.5 h; (d) TBDPSCl, DMF, imidazole, 55°C, 5 h; (e) DIBAL-H (1.2 eq), tol., -78°C, 15 min; (f) $CH{\equiv}CCH_2Br$, Zn, THF, -15°C, 1 h; then **11**, THF, -30°C, 45 min; (g) TBS triflate, 2,6-lutidine, CH_2Cl_2, 0°C, 0.5 h; (h) n-BuLi, THF, -78°C → 0°C, 2 h; then $(CH_2O)_3$, 0°C, 3 h; (i) Red-Al (2.3 eq), Et_2O, 0°C → r.t.,4 h; then EtOAc (1 eq); then I_2 (2 eq), THF, -78°C, 0.5 h; -78°C → r.t., 1 h; (j) $Pd(PPh_3)_4$ (5 mol %), Et_3N (10 eq), MeCN, 55°C, 4 h; (k) NaOMe, 0°C, 12 h.

Scheme 2

As preliminary results obtained on racemic **8a** had shown that DIBAL-H reduction was possible only on silyl-protected form, acetate **9** was first transformed into TBDPS ether **10** prior to reduction to aldehyde **11**.

For the construction of the desired *anti* diol configuration the method involving a chiral allenylboronic ester[12] was first investigated. However this led in low yield (45 %) to *anti*-syn mixture in 2:1 ratio. The 3-C homologation step was therefore carried out in a non-selective manner using allenylzinc bromide[13] affording in high yield **12**[14] and 5-*epi* **12** in a 7:4 ratio. Fortunately facile preparative HPLC separation was possible, giving pure **12a** in 61 % isolated yield. It is noteworthy that purification of the alternative TBS ether **12b** was much more difficult. Finally protection led to the first target **4b** in 21 % overall yield (7 steps)[15] from **7**.

The 1,7 enyne **4b** is a key-intermediate for the synthesis of allylic alcohol **15a**; the exocyclic diene with Z-geometry will be formed upon an intramolecular Heck reaction[16] of the Z-vinyl iodide **14**. Hydroxymethylation of alkyne **4b** afforded the propargylic alcohol **13** which upon Denmark's[17] modification of Corey's[18] reductive iodination method led to intermediate **14**. The conditions for this step are rather critical; a yield of 77% was obtained when 2.3 eq. Red-Al was used followed by carefully destroying the excess with ethyl acetate (1 - 1.2 eq; dried on molecular sieves) before freshly sublimed iodine was added.[19] The Pd-catalyzed cyclization[20,21] of **14** gave **15a**. Deprotection of a sample of **15a** gave **15b**[22], identical with the triol obtained upon deprotection of **2a**, prepared from S-carvone[4]. Transformation of **15a** into **2b** was carried out as described for **2a** in the above mentioned synthesis.[4] The desired phosphine oxide **2b** is thus available in 12 steps from acroleine in 9 % overall yield. The two differently protected hydroxyl groups in **2b** could allow eventual selective manipulations of these functions for the synthesis of other A-ring analogues of **1**.



(a) LDA, *t*-BuOAc, THF, -78°C → 0°C, 4 h; (b) $Me_4NHB(OAc)_3$, MeCN, 0°C, 5 h; (c) TBSCl, DMF, imidazole, r.t., 15 h; (d) DIBAL-H (1.7 eq), tol., -78°C; (e) CBr_4, Ph_3P, Zn, tol., -78°C; (f) *n*-BuLi, $(CH_2O)_3$, THF, -78°C → r.t.

Scheme 3

In order to bypass the reaction on intermediate **11**, an alternative approach for A-ring precursor **2a**, starting from **8b**, was investigated in the racemic series (Scheme 3). Claisen condensation of **8b** gave β-keto ester **16** which upon stereoselective *anti*-reduction[23] with $Me_4NBH(OAc)_3$ provided diol **17**[24] in 80% d.e. Protection of the hydroxy groups and DIBAL-H reduction afforded aldehyde **18** (55% over the three steps).

Transformation from **18** to **19** was carried out in a two step operation: (i) Wittig type[25] conversion to the corresponding *gem* vinyl dibromide and (ii) reaction of this product with *n*-BuLi and trapping of the resulting acetylide with trioxane. The remaining steps are identical as described for **2b** from **13**.

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