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A Novel Entry to the Vitamin D Triene System

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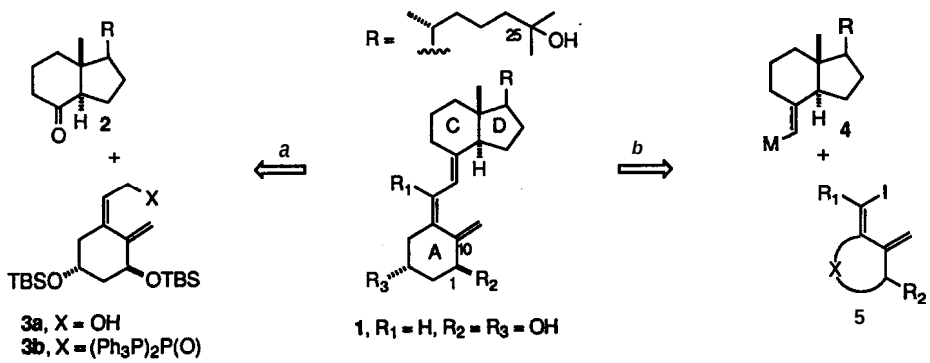
Abstract. The application of Negishi's cyclixation methodology to the synthesis of (Z)-1-iodo-1,3-bisexocyclic-dienes from acyclic precursors is described. This kind of compounds can be used for the preparation of conjugated systems such us the triene of vitamin D.

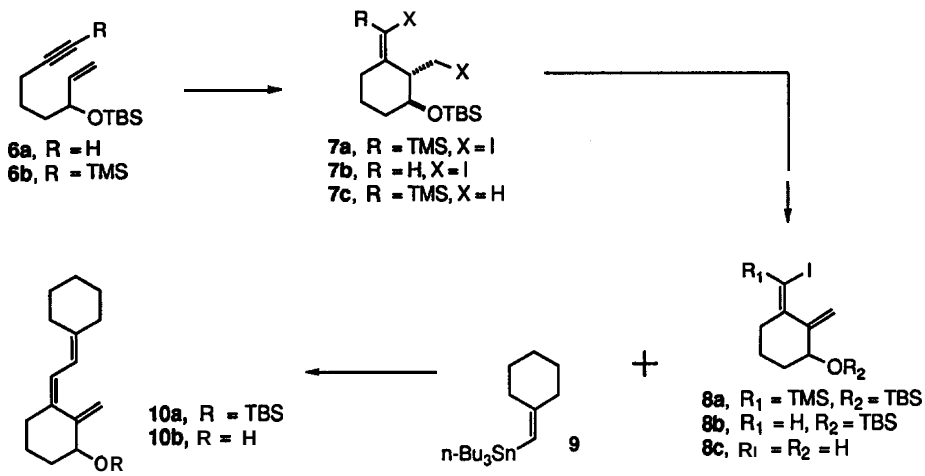
The discovery that **1α,25-dihydroxyvitamin D3 (1),** the hormonally active form of vitamin **D3,** plays an important function in a number of fundamental cell processes (including cell differentiation and proliferation) in addition to its classical role in calcium homeostasisl has renewed interest in the synthesis of analogues with potential therapeutical utility in the treatment of proliferative disorders, or which can be used to investigate the molecular mechanism of action of the hormone.[2] Among the reported synthetic approaches to the triene system of vitamins D, those based on convergent strategies have been shown to be the most useful and versatile since they allow for separate elaboration of the C/D-side chain and ring A fragments.3 There have recently been published several elegant routes to the alcohol **3a,** a fragment required for the synthesis of **1** by Wittig-Homer coupling of its phosphme oxide derivative **3b** with the corresponding upper part ketone 2 (route a, scheme I).[4] Although this strategy is highly efficient for the synthesis of a variety of C/D-side chain analogues of the hormone **1,** it seems less suitable for the preparation of derivatives with a modified ring A and/or triene system.[5,6]



Scheme I

We hypothesized that these latter analogues might be more accessible via a palladium catalyzed coupling between suitably prepared (Z)-vinyliodides, like 5, and fragments of type 4 (M = ZnBr, Bu_3Sn or others), i.e. route *b* of Scheme I.7 Here we report the results of our initial efforts towards this goal, the stereoselective synthesis of (Z)- 1-iodovinyl *bis*-exocyclic 1,3-cyclohexanedienes **8a-c** from readily available acyclic precursors and their coupling with the model vinylstannane 9 to give the triene system present in vitamin D.

The synthesis is based on the previously described zirconium-promoted cyclization of 1,7-enynes.[8] The required enyne precursor **6b** (Scheme II) was prepared by treatment of enyne **6a**[5d] with methyllithium and trapping of the resulting acetylide with TMSCl. Under previously described conditions for the cyclization-iodonolysis sequence [(a) Cp_2ZrCl_2, *n*-BuLi, THF. (b) I_2, THF],[8] compound **7a** was obtained in 55% yield (87% based on recovered starting material). Other iodinatlng agents (*N*-iodosuccinimide and 1,2-diiodoethane) did not provide better yields. The stereochemistry was assigned on the basis of previously reported data for compound **7c**.[8c] The absence of observable ^1H NMR coupling between H-l and H-10 (steroidal numbering) is consistent with their lying equatorial9



Scheme II

The exocyclic double bond was efficiently introduced by treatment of **7a** with DBU in CH_2Cl_2 (r.t., 3 days, 90% yield),[10] and the trimethylsilyl group was smoothly removed by reaction of **8a** with Cs_2CO_3 in DMF (r.t., 12 h, 84 % yield). Compound **8b** was alternatively obtained by inverting the procedure: initial treatment of **7a** with Cs_2CO_3 in DMF (or stirring with KF in CH_3CN) to remove the trimethylsilyl group, and subsequent elimination with DBU in CH_2Cl_2 (82% yield for both steps). Most importantly, compound **7a** can be transformed in a one-pot reaction to the requited vinyliodide **8c** by treatment with TBAF (3 equiv) in THF at room temperature (83% yield). The Q-stereochemistry of compound **8c** was confirmed by NOE ^1H NMR spectroscopy.[11] Silylation (TBSCl, imidazole, DMF) afforded a compound that was spectroscopically identical to compound **8b** obtained by the above procedures. To test whether these iodovinyl compounds **8** can be used to prepare the conjugated triene system of vitamins D, the cross-coupling reaction of **8b** with the vinyhributyltin

derivative **9**[12] under Stille conditions was performed. Stirring a solution of compound **8b** and 9 (2 equiv) in DMF and in the presence of $Pd(CH_3CN)_2Cl_2$ (5%)[7] for two days at **room temperature** followed by desilylation (TBAF, THF) afforded a compound whose ^1H NMR is identical to that of **10b**[13] (53% over the two steps, unoptimized yield). This compound was also obtained by direct coupling between 9 and **8c** under the same reaction conditions (50% unoptimized yield).[14] Work to prepare the required true upper fragment 4, and optically active ring A derivatives, is underway.

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