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Pd-Catalyzed Carbocyclization–Negishi Cross-Coupling Cascade: A Novel Approach to 1α,25-Dihydroxyvitamin D_3 and Analogues†

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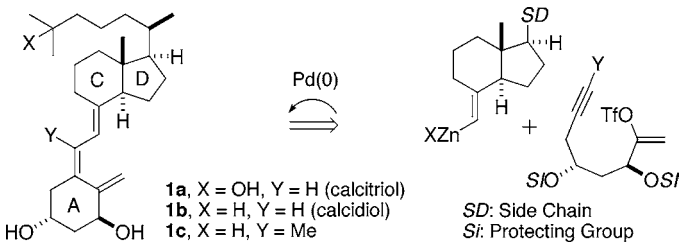
ABSTRACT



A mild palladium-catalyzed cascade has been used for the synthesis of the hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, 1a) and its analogues 1b and 1c. This one-pot process involves two consecutive transformations at room temperature: An initial palladium-catalyzed 6-exo-cyclocarbopalladation of vinyl triflates followed by a Negishi cross-coupling reaction with an alkenyl zinc. This novel strategy opens new possibilities for the preparation of a variety of new vitamin D analogues of therapeutic potential, particularly with modifications at the triene and/or ring-A.

The steroid hormone 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2$-D_3, calcitriol, **1a**) is the bioactive metabolite of vitamin D_3. This B-ring-seco-steroid plays an important role in the regulation of mineral metabolism and finds application in the treatment of osteodystrophy due to renal failure, rickets, osteoporosis, and psoriasis. The current interest in the therapeutic properties of 1α,25-$(OH)_2$-D_3 and its 1α-hydroxyvitamin D_3 analogues results from the ability of these compounds to control abnormal processes by modulating cell differentiation, inhibiting cell proliferation, and regulating apoptosis, characteristics that suggest their use in the treatment of cancer and other proliferative diseases.[1] Efforts aimed at developing vitamin D analogues with strong cell-differentiating ability and low calcemic action have led to the synthesis of more than 3000 vitamin D analogues, and some of these are already on the market and in clinical development.[2−4]

The increasing number of potential therapeutic applications of 1α,25-$(OH)_2$-D_3 and its 1α-hydroxyvitamin D analogues has stimulated extensive synthetic efforts from several laboratories over the past 25 years.[5] The continued need for the synthesis of new 1α-hydroxyvitamin D analogues with biological activities comparable or superior to 1α,25-$(OH)_2$-

† Dedicated to Prof. William Okamura.
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(1) (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: San Diego, CA, 1997. (b) *Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; University of California: Riverside, CA, 2000. (c) First International Conference on Chemistry and Biology of Vitamin D Analogs. *Steroids* **2001**, *66*, 127−471.

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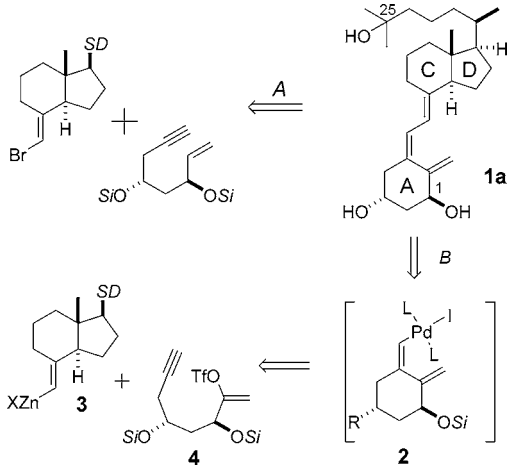
D_3 is the driving force for the development of new synthetic strategies. Current synthetic methodologies can be classified into three main types. The classical approach involves photochemical ring opening of a steroid precursor,[6] a route that does not work well for the synthesis of 1α-hydroxyvitamin D analogues. More efficient approaches are based on convergent methodologies in which a preformed ring-A fragment is attached to a CD fragment.[4,7] A wide variety of routes to this ring-A synthon have been reported.[4,5a] More recently, Trost and co-workers have developed a new convergent route in which the ring-A and triene unit are formed by Pd(0)-catalyzed alkylation−cyclization reactions starting from an acyclic unit and a vinyl bromide[8] (route A, Scheme 1). This approach is being successfully employed

Scheme 1. Trost Approach (A) and New Retrosynthetic Analysis (B) of 1α,25-$(OH)_2$-D_3[a]



[a] Si = Protecting group. SD = Side chain.

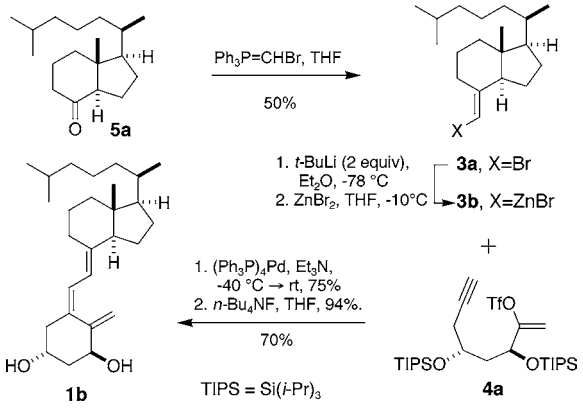
for the preparation of 1α-hydroxyvitamin D analogues modified at the ring-A.

We wish to report a new, highly efficient convergent strategy to 1α,25-$(OH)_2$-D_3 and its analogues in which ring-A and triene unit are constructed by one-pot Pd-catalyzed tandem cyclization−Negishi coupling process involving an alkenyl zinc intermediate (**3**) and a vinyl triflate (**4**) (route B, Scheme 1).[9]

On the basis of the results of previous work,[7e] we envisioned that the triene system of 1α,25-$(OH)_2$-D_3 and its 1-hydroxylated analogues could be formed by a palladium-catalyzed cascade involving a carbometalation−cyclization process starting from vinyl triflate **4** followed by cross-coupling of the resulting Pd(II) intermediate **2**[10] with the alkenyl zinc derivative **3**.

Calcidiol (**1b**) was selected as our initial target (Scheme 2) to assess the viability of the new convergent strategy and

Scheme 2. Convergent Synthesis of Calcidiol (**1b**)



for synthetic simplicity. The bromoolefin **3a** was prepared from Grundmann's ketone (**5a**) according to Trost's procedure.[8]

Vinyl triflate **4a** was prepared in 45% yield from *l*-carvone as described previously.[11] Metalation of the alkenyl bromide **3a** with *tert*-butyllithium and subsequent transmetalation with zinc dibromide provided the organozinc derivative **3b**. The carbometalation−cyclization−Negishi cross-coupling cascade to the vitamin D triene unit was performed as follows. A solution of vinyl triflate **4a** (1 equiv), triethylamine (3 equiv), and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) was added to a solution of the organozinc derivative **3b** (2 equiv) in THF at −40 °C. The reaction mixture was stirred for 15 min and then allowed to reach room temperature. The residue was purified by flash chromatography (SiO_2) to provide, after desilylation, the desired calcidiol (**1b**) (75% from **3a**).

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(6) (a) Schmalz, H.-G.; Walzer, E. *Vitamin D Active Compounds*; Quinkert, G., Ed.; VCH Verlagsgesellschaft mbH: Weinheim, Germany, **1985**, Vol. 3, pp 41−122. (b) Schmalz, H.-G.; Walzer, E. *Vitamin D Active Compounds Part II*; Quinkert, G., Ed.; VCH Verlagsgesellschaft mbH: Weinheim, Germany, **1986**, Vol. 4, pp 131−258. (c) Schmalz, H.-G.; Walzer, E. *Vitamin D Active Compounds Part III*; Quinkert, G., Ed.; VCH Verlagsgesellschaft mbH: Weinheim, Germany, **1987**, Vol. 5, pp 1−86.

(7) For selected examples, see: (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098−3108. (b) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *20/21*, 3485−3489. (c) Pérez-Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 118−123. (d) VanAlstyne, E. M.; Norman, A. W.; Okamura, W. H. *J. Am. Chem. Soc.* **1994**, *116*, 6207−6216. (e) García, A. M.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6353−6358. (f) Hanazawa, T.; Koyama, A.; Wada, T.; Morishige, E.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 523−525.

(8) (a) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924−1925. (b) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836−9845.

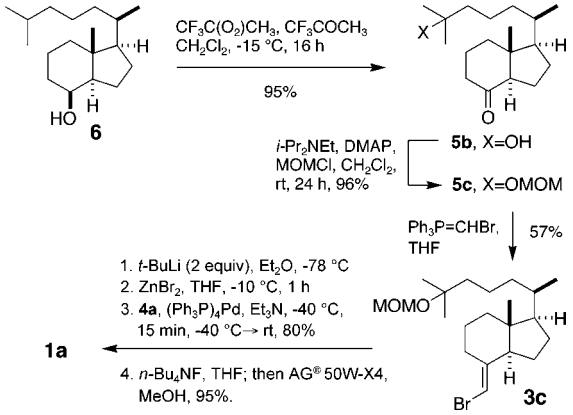
(9) For a related 5-exo-dig cyclocarbopalladation-Stille cross-coupling process, see: Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 2307−2310.

(10) Previous work in our laboratory led to an efficient approach to 3-deoxy-1-hydroxyvitamin D_3 analogues employing a Pd(0)-catalyzed coupling between an alkenyl iodide and an alkenyl zinc intermediate. This process presumably proceeds via palladium intermediates of type **2**. Unfortunately, the formation of the vinyl iodide corresponding to ring A of 1α,25-$(OH)_2$-D_3 through metal-induced cyclization on the 3-hydroxyl-protected enyne precursor was unsuccessful.

(11) The corresponding *tert*-butyldimethyl silyl-protected vinyl triflate was used in our laboratories for the construction of Lythgoe Ring-**A** phosphine oxide. Mouriño, A.; Torneiro, M.; Vitale, C.; Fernández, S.; Pérez-Sestelo, J.; Anné, S.; Gregorio, C. *Tetrahedron Lett.* **1997**, *38*, 4713−4716.

The success of the new strategy led us to undertake the synthesis of the natural hormone calcitriol (**1a**) (Scheme 3).

Scheme 3. Synthesis of Calcitriol (**1a**)

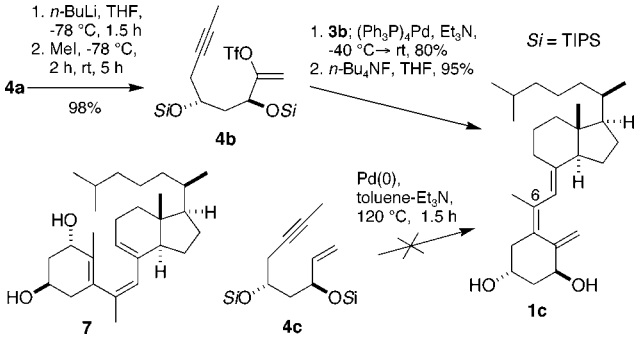


Alcohol **6** was obtained in 84% yield by degradation (O_3; $NaBH_4$) of commercially available vitamin D_3 according to a known procedure.[12] Remarkably, exposure of **6** to methyl(trifluoromethyl)dioxirane[13] furnished directly 25-hydroxy Grundmann's ketone (**5b**) in 95% yield without noticeable epimerization at C-14.[14] Protection of **5b** as the methoxymethyl ether followed by bromoolefination as above provided the alkenyl bromide **3c** (57%, two steps). The bromoolefin **3c** was subjected to sequential metalation and transmetalation to give the corresponding organozinc derivative, which was treated with vinyl triflate **4a** to give, by the palladium-catalyzed cascade and deprotection, the desired hormone 1α,25-(OH)$_2$-D_3 (76%, three steps from **3c** or 41% in six steps from alcohol **6**). Spectral data for this compound are identical to those of the material obtained by a different route.[7b,c]

The scope and potential of the new convergent synthetic approach was assessed by aiming for the 1α-hydroxy-6-methyl-vitamin D_3 analogue (**1c**, Scheme 4) as the synthetic target. Analogues of the natural hormone with substituents at the triene system have rarely been prepared due to synthetic difficulties associated with the current available synthetic routes.[15] Furthermore, the presence of a methyl group at position 6 of vitamin D_3 is known to considerably decrease the energetic barrier to its isomerization to the previtamin D form.[7e,15a] For this reason, the success in the synthesis of this type of derivative would give an indication of the mildness of the new approach to prepare thermally sensitive analogues.

Metalation of **4a** followed by alkylation provided the vinyl triflate **4b** in 98%. Gratifyingly, the palladium-catalyzed process involving **4b** and **3b** proceeded *at room temperature* to give, after removal of the silyl-protecting groups, the desired vitamin D_3 analogue **1c** in 78% yield (two steps). As expected, the 6-methylvitamin D_3 analogue **1c** showed a great propensity to isomerize to the corresponding previtamin D_3 form **7**. The isomerization equilibrium was reached upon heating a solution of **1c** in CD_3OD at 40 °C for 12 h. The ratio of vitamin−previtamin forms was 10:90 as determined by ^{1}H NMR integration of the respective 18-CH_3 signals.

Scheme 4. Synthesis of 1α-Hydroxy-6-methyl-vitamin D_3 (**1c**)



For comparative purposes, we heated a mixture of enyne **4c** (see Supporting Information) and alkenyl bromide **3a** under Trost Pd-catalyzed alkylative enyne cyclization conditions ((dba)$_3$Pd$_2$·CHCl$_3$, Ph$_3$P, toluene−Et$_3$N, 120 °C, 1.5 h).[8] Not surprisingly, only starting materials were recovered regardless of reaction conditions. The failure of triene formation in this case can be attributed to the acetylenic methyl group of **4c**, which imparts a higher steric hindrance to the triple bond.

In summary, we have carried out the synthesis of 1α,25-dihydroxyvitamin D_3 (calcitriol, **1a**) and its analogues 1α-hydroxyvitamin D_3 (calcidiol, **1b**) and 1α-hydroxy-6-methyl-vitamin D_3 (**1c**). The key step in the successful, novel, mild, and stereoconvergent strategy was a cascade process consisting of two consecutive transformations: An initial palladium-catalyzed 6-exo-cyclocarbopalladation of vinyl triflates followed by a Negishi cross-coupling reaction with an alkenyl zinc. Further extension of this approach to the rapid synthesis of a variety of new vitamin D_3 analogues of therapeutic potential, especially those modified at the triene and ring-A, is underway.

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Supporting Information Available: Experimental procedure and ^{1}H and ^{13}C spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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