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An Expeditious Route to 1α,25-Dihydroxyvitamin D_3 and Its Analogues by an Aqueous Tandem Palladium-Catalyzed A-Ring Closure and Suzuki Coupling to the C/D Unit

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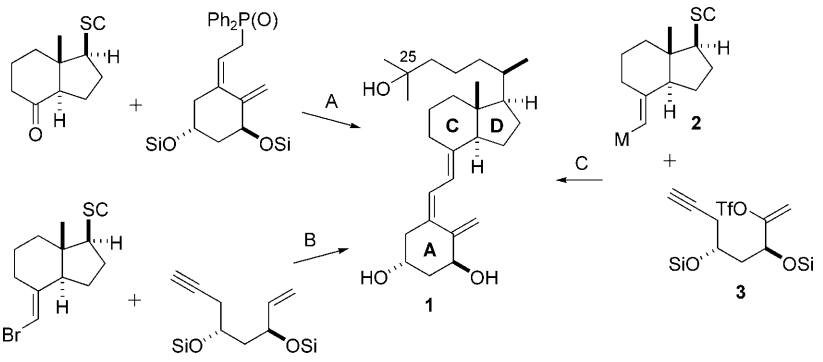
Dedicated to Professor Dieter Seebach

1α,25-Dihydroxyvitamin D_3 (**1**), the hormonally active metabolite of the *seco*-steroid vitamin D_3, interacts with the vitamin D nuclear receptor (VDR)[1] to initiate a cascade of events that ultimately controls mineral homeostasis and a multitude of cellular processes including differentiation, antiproliferation, growth, apoptosis, angiogenesis, and immunomodulation.[2] Unfortunately, the therapeutic applications of **1** in pharmacological doses to correct dysfunction of one or more of these processes are severely limited by its potent calcemic effects.[3] Efforts to develop analogues with selectively reduced calcemic effects for treatment of, for example, cancer and skin diseases or with selective activity on bone formation have led to more than 3000 synthetic analogues being tested, although only a few have reached the pharmaceutical market or advanced clinical trials.[4]

The most useful convergent methods to synthesize the triene moiety in vitamin D analogues include the Wittig–Horner approach devised by Lythgoe and developed by the Hoffmann La Roche group (Scheme 1, route A)[5] and the palladium-catalyzed route introduced by Trost and co-workers (Scheme 1, route B).[6] These methods have practical drawbacks in that they either require an excess of the lower (A ring) fragment (for small-scale work) or elevated temperatures that equilibrate vitamin D with its previtamin D form. We have recently also developed a palladium-catalyzed process for the construction of the vitamin D triene that couples enol–triflates with alkenyl zinc intermediates (Scheme 1, route C), but this method was still limited by problems with reproducibility on the small-scale and requires two equivalents of the upper (C/D) fragment even to afford moderate yields.[7,8]



Scheme 1. Synthetic routes to vitamin D compounds. M = metal, SC = side chain, Si = protecting group.

Prompted by these considerations and the continuing need for simple, small-scale access to an array of test compounds for rapid screening to generate clinical candidates, we envisaged the possibility of employing alkenyl-boronic esters (**2**, $M = B(OR)_2$; Scheme 1), instead of the corresponding alkenyl zinc intermediates of our earlier work.[9] A Suzuki coupling with the palladium intermediate resulting from the initial cyclization of enol–triflate **3a**[10] as a precursor of the A-ring fragment would construct the triene unit

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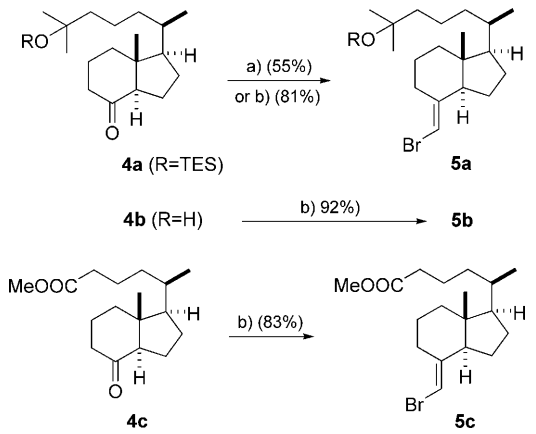
stereoselectively in one pot. We can now report that this strategy does indeed circumvent the problems associated with the previous synthetic approaches and provides a general method for the small-scale preparation of a wide variety of vitamin D analogues in a practical, economical, and reproducible fashion.

To validate the approach, we were first concerned with the synthesis of the natural hormone **1**. Our synthesis commences with the known alkenyl bromide **5a** that is derived from ketone **4a** in ≈55% yield by using Trost conditions (Scheme 2).[6] The moderate yield in the Wittig reaction

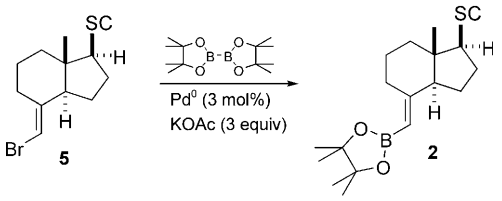


Scheme 2. Synthesis of alkenyl bromides **5a–c**. TES = $SiEt_3$. a) Trost conditions: $Ph_3P^+CH_2BrBr^-$, NaHMDS (HMDS = hexamethyldisilazane), THF; b) new conditions: $Ph_3P^+CH_2BrBr^-$ washing with toluene/CH_2Cl_2 under ultrasonication, then KO*t*Bu, −15→0°C.

prompted us to scrutinize this important step, and eventually we found that purification of the phosphonium salt by washing with toluene/CH_2Cl_2 under sonication, followed by generation of the ylide with KO*t*Bu in toluene (instead of the previously used NaHMDS in THF) and subsequent reaction with ketones **4a–c**, which incorporate diverse functionally at the side chains, provided the corresponding alkenyl bromides **5a–c** in good yields.

The alkenyl bromide **5a** could be converted to boronate **2a** by lithiation–transmetallation according to a procedure reported by Sato and co-workers,[11] but the fact that this reaction sequence is not compatible with functionalities such as the hydroxy and ester groups present in alkenyl bromides **5b** and **5c** led us to explore better procedures for this transformation. We first studied the conditions developed by Miyaura and co-workers that were previously used to prepare arylboronic esters by a Pd^0-catalyzed cross-coupling reaction between bis(pinacolato) diboron and haloarenes.[12] However, these conditions afforded the desired boronate **2a** in low yields (Table 1, entries 1–3). After several attempts using different catalysts and ligands, we finally found that the use of tricyclohexylphosphine (PCy_3) as the ligand together with the Miyaura catalyst provided boronate ester **2a** in excellent yield (Table 1, entry 8), and furthermore

Table 1. Pd^0-catalyzed preparation of alkenyl boronates **2** from alkenyl bromides **5**.[a]

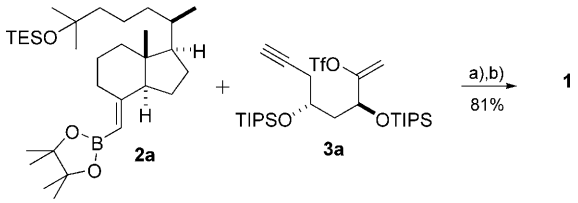


Entry	Substrate	Catalyst	Ligand	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	**5a**	$[PdCl_2(Ph_3P)_2]$	PPh_3	toluene	50	6	0[c]
2[d]	**5a**	$[PdCl_2(dppf)]$	–	DMSO	80	6	35
3	**5a**	$[Pd_2(dba)_3]$	PCy_3	dioxane	80	12	23
4[d]	**5a**	$[PdCl_2(dppf)]$	PCy_3	DMSO	RT	12	28
5	**5a**	SK-CC02A	–	dioxane	80	12	28
6	**5a**	SK-CC02A	–	DMSO	80	6	68
7[d]	**5a**	$[PdCl_2(dppf)]$	PCy_3	dioxane	80	6	60
8[d]	**5a**	$[PdCl_2(dppf)]$	PCy_3	DMSO	80	3	91
9[d]	**5b**	$[PdCl_2(dppf)]$	PCy_3	DMSO	80	3	92
10[d]	**5c**	$[PdCl_2(dppf)]$	PCy_3	DMSO	80	3	80

[a] dba = *trans,trans*-dibenzylideneacetone. dppf = 1,1′-bis(diphenylphosphino) ferrocene. SK-CC02A = 2-(dimethylaminomethyl)ferrocen-1-ylpalladium(II) chloride dinorbornylphosphine complex. PCy_3 = tricyclohexylphosphine. DMSO: dimethylsulfoxide. [b] Isolated yields. [c] KOPh (1.5 equiv). [d] Catalyst complexed to CH_2Cl_2.

worked equally well with alkenyl bromides **5b,c** to give boronate esters **2b,c** (Table 1, entries 9 and 10).

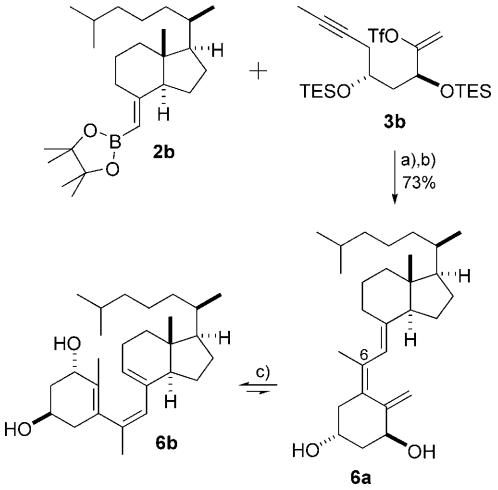
With **2a** and **3a** in hand, we proceeded to the critical Pd-catalyzed tandem cyclization–Suzuki coupling process to the triene system of the natural hormone **1**. Treatment of a mixture of **2a** (0.23 mmol) and **3a** (0.27 mmol) in aqueous K_3PO_4 (2 M)/THF with a catalytic amount of $[PdCl_2(Ph_3P)_2]$ (5 mol%) at RT for 1 h delivered, after standard desilylation, the natural hormone **1** in 81% yield (Scheme 3). Any



Scheme 3. Synthesis of the natural hormone **1**: a) $[PdCl_2(Ph_3P)_2]$ (5 mol%), 2 M K_3PO_4 (aq)/THF, RT, 1 h; b) nBu_4NF, THF, RT, 24 h. TIPS = $Si(iPr)_3$.

problems associated with excess of one or the other synthetic building block, exclusion of moisture, and/or elevated temperature are dismissed in this remarkable reaction, and the way is opened up for making analogues with modified structures under these standard conditions.[13]

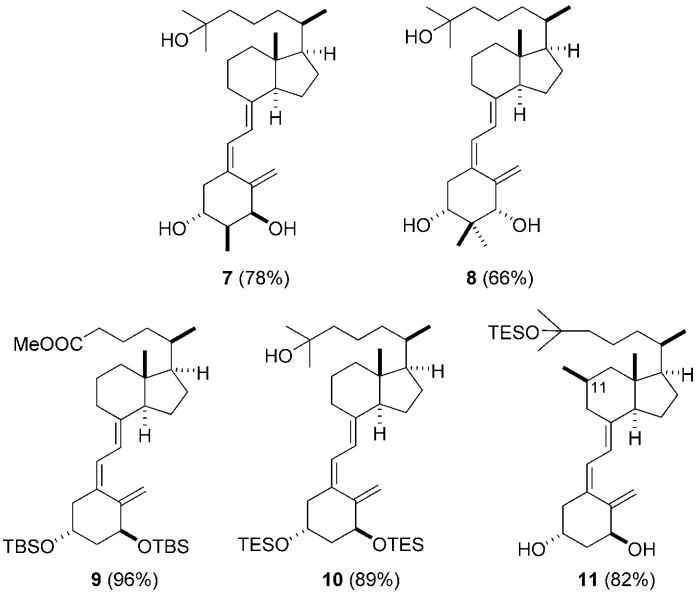
The 6-methyl-derivative **6a**, which could not be prepared by routes A[14] or B,[7] was selected as a test for our methodology (Scheme 4). Gratifyingly, enyne **3b**[7] reacted with **2b** under the standard conditions to give the target compound **6a** in 73% yield after desilylation. The mildness of the



Scheme 4. Synthesis of 1α-OH-6-methyl-vitamin D_3: a) standard conditions; b) nBu$_4$NF, THF, RT, 2 h (73% yield for the two steps); c) equilibration time in CD_3OD at RT and ratio vitamin D/previtamin D determined by ^{1}H NMR spectroscopy: (3 d, **6a**/**6b** = 1/1; 15 d, **6a**/**6b** = 1/60).

method is strikingly demonstrated by the fact that analogue **6a** equilibrates on standing in CD_3OD with its previtamin D form **6b**.

The versatility and flexibility of the new route is illustrated by the efficient construction of the triene moieties of the variety of vitamin D analogues shown in Scheme 5. As representative examples of analogues modified at the A ring, we prepared **7**[15] (78% yield) (a member of the superagonist set of analogues) and **8**[16] (66%) (which has a congested A-ring fragment). For examples with other functionalities at the side chain we chose compounds **9** and **10**. Compound **11** was chosen as the test example of a vitamin D analogue modified at the C ring, since the original synthesis of analogues with a β-substituent at C-11 in Vandewalle's laboratory provided consistently low yields (20–40%) by the Wittig–Horner approach (Scheme 1, route A).[17]



Scheme 5. Illustrative examples of vitamin D analogues modified at the A ring, C ring, and side chain. Yields for the two steps, Pd-catalyzed cyclization-coupling and desilylation, are shown in parentheses. No desilylation was carried out for examples **9**, **10**, and **11**. TBS = SiMe$_2$$t$Bu.

In summary, a concise, general, and stereoselective entry to the vitamin D triene system of the natural hormone **1** and six representative analogues has been achieved by an efficient strategy featuring a highly stereoselective intramolecular cyclization of an enol triflate (A ring or lower fragment) followed in situ by a Suzuki–Miyaura coupling of the resulting palladium intermediate with an alkenyl boronic ester (CD side-chain upper fragment). The method employs equimolar quantities of both fragments under protic conditions and can be used for the preparation of small amounts of new vitamin D analogues for biological testing. Further synthetic studies pertaining to even more challenging vitamin D analogues are underway in our laboratory.

Acknowledgements

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Keywords: homogeneous catalysis · natural products · palladium · synthesis design · vitamins

[1] a) N. Rochel, J. M. Wurtz, A. Mitschler, B. Klaholz, D. Moras, *Mol. Cell* **2000**, *5*, 173–179; b) S. Christakos, P. Dhawan, B. Benn, A. Porta, M. Hediger, G. T. Oh, E. B. Jeung, Y. Zhong, D. Ajibade, K. Dhawan, S. Joshi, *Ann. N. Y. Acad. Sci.* **2007**, *1116*, 340–348.

[2] a) *Vitamin D* (Eds.: D. Feldman, F. H. Glorieux, J. W. Pike). Elsevier, New York, **2005**; b) "Proceedings of the 12th and 13th Workshop on Vitamin D" (Eds.: R. Bouillon, A. W. Norman, J. R. Pasqualini): *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 201–822; **2004**, 89–90, 1–633; and the previous 11 volumes in these series.

[3] a) M. S. Stein, J. D. Wark, *Expert Opin. Invest. Drugs* **2003**, *12*, 825–840; b) K. K. Deeb, D. L. Trump, C. S. Johnson, *Nat. Rev. Cancer* **2007**, *7*, 684–700.

[4] a) M. M. Kabat, R. Radinov, *Curr. Opin. Drug Discov. Devel.* **2001**, *4*, 808–833; b) A. J. Brown, *Am. J. Kidney Dis.* **2001**, *38*, S3–S19; c) C. Carlberg, A. Mouriño, *Expert Opin. Ther. Pat.* **2003**, *13*, 761–772; d) R. Bouillon, W. H. Okamura, A. W. Norman, *Endocr. Rev.* **1995**, *16*, 200–257.

[5] E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy, A. D. Batcho, J. F. Sereno, M. R. Uskokovic, *J. Org. Chem.* **1986**, *51*, 3098–3108.

[6] B. M. Trost, J. Dumas, M. Villa, *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

[7] C. Gómez-Reino, C. Vitale, M. Maestro, A. Mouriño, *Org. Lett.* **2005**, *7*, 5885–5887.

[8] For selected reviews on the synthesis of vitamin D compounds, see: a) G.-D. Zhu, W. H. Okamura, *Chem. Rev.* **1995**, *95*, 1877–1952; b) S. Krause, H.-G. Schmalz, *Organic Synthesis Highlights* (Ed.: H.-G. Schmalz), Wiley-VCH, Weinheim, **2000**, pp. 212–217; c) G. H. Posner, M. Kahraman, *Eur. J. Org. Chem.* **2003**, 3889–3895.

[9] a) A. M. García, J. L. Mascareñas, L. Castedo, A. Mouriño, *J. Org. Chem.* **1997**, *62*, 6353–6358; b) A. M. García, J. L. Mascareñas, L.

Castedo, A. Mouriño, *Tetrahedron Lett.* **1995**, *36*, 5413–5416; c) J. L. Mascareñas, A. M. García, L. Castedo, A. Mouriño, *Tetrahedron Lett.* **1992**, *33*, 7589–7592.

[10] A. Mouriño, M. Torneiro, C. Vitale, S. Fernández, J. Pérez-Sestelo, S. Anne, C. Gregorio, *Tetrahedron Lett.* **1997**, *38*, 4713–4716.

[11] T. Hanazawa, A. Koyama, K. Nakata, S. Okamoto, F. Sato, *J. Org. Chem.* **2003**, *68*, 9767–9772.

[12] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510.

[13] For reviews on Suzuki–Miyaura coupling reactions, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) N. Miyaura, *J. Organomet. Chem.* **2002**, *653*, 54–57.

[14] Unpublished results from our laboratory.

[15] Compound **7** was synthesized in 67% yield by the Trost method: K. Konno, S. Maki, T. Fujishima, Z.-P. Liu, D. Miura, M. Chokki, H. Takayama, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 151–156.

[16] Compound **8** was synthesized by the Trost method in 63% yield as a mixture with its 3-epimer: T. Fujishima, A. Kittaka, K. Yamaoka, K. Takeyama, S. Kato, H. Takayama, *Org. Biomol. Chem.* **2003**, *1*, 1863–1869.

[17] R. Bouillon, K. Allewaert, J. P. T. M. van Leeuwen, B.-K. Tan, D. Z. Xiang, P. De Clercq, M. Vandewalle, H. A. P. Pols, M. P. Bos, H. van Baelen, J. C. Birkenhäger, *J. Biol. Chem.* **1992**, *267*, 3044–3051.

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