Pergamon

Tetrahedron Letters, Vol. 36, No. 30, pp. 5413-5416, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00993-0

A Mild Palladium-Catalysed Convergent Approach to the Vitamin D Skeleton[1]

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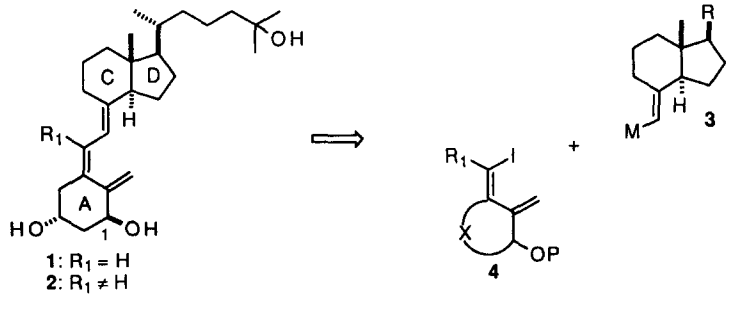
Abstract: Palladium-catalysed cross-coupling of (*Z*)-1-iodo-1,3-*bis*-exocyclic dienes and alkenyl-zinc reagents bearing the C,D-ring/side chain portion provides a new efficient entry to the tricyclic system of vitamin D.

An increasing body of evidence suggests that the hormone 1α,25-dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, Scheme 1], in addition to its classical functions in calcium and phosphorus metabolism, regulates the proliferation and differentiation of a large variety of immunological and malignant cells.[2] Therefore, a great deal of current research in the vitamin D area is aimed at development of non-toxic derivatives of this hormone as potential agents for treatment of hyperproliferative diseases such as psoriasis and cancer, and of inmunological conditions such as autoimmune diseases and graft rejection.[2,3] Current approaches to the vitamin D skeleton have been successfully applied to the synthesis of a wide range of analogues of **1** modified at the C,D-ring, side chain or A-ring portion, but have proved less valuable for synthesis of derivatives in which the triene system bears substituents (for instance **2**).[4] Since this type of analogues might prove very useful for evaluation of the role of the triene system with respect to the biological profiles,[5] and also for further study of chemical issues related to the classical vitamin-previtamin isomerization,[6] we have explored novel approaches to the vitamin D skeleton that might allow the synthesis of such compounds.

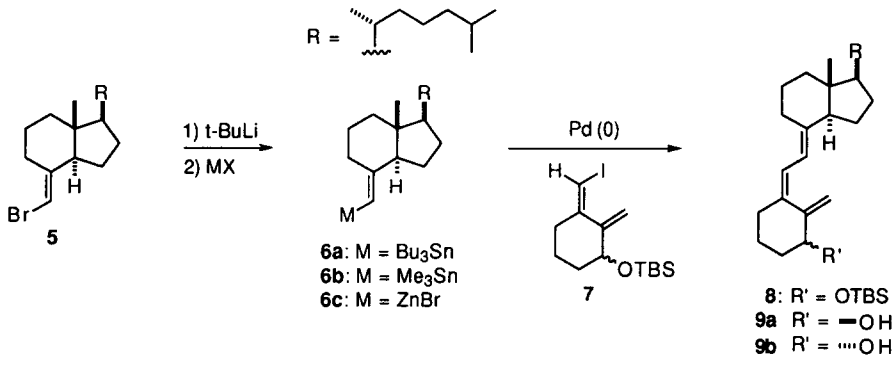
Our efforts have led to the development of a new strategy that relies on the convergent construction of the conjugated triene unit of vitamin D by means of Pd-catalysed cross-coupling of organometallic C,D-ring/side chain fragments (**3**) and A-ring iododiene units (**4**) derived from acyclic precursors (Scheme 1).



Scheme 1

Following the success of our preliminary experiments on Pd-catalysed coupling between A-ring iododiene units and simple alkenyltributylstannanes to produce the characteristic vitamin D triene system,[7] we proceeded to investigate the coupling of vinyliodide **7**, which bears the biologically critical 1-hydroxyl group, with the stannane **6a** with the naturally occuring skeleton (C/D ring-side chain).

Compound **6a** was prepared by treating vinylbromide **5**[8] with *t*-BuLi and trapping the resulting anion with tributyltin chloride (85 % yield). Unfortunately, several attempts at cross-coupling **6a** and vinyliodide **7**,[7] using a variety of catalyst, solvent, and temperature combinations, all failed (Table 1).[9] However, by using the less sterically demanding trimethyltin derivative **6b** as organometallic partner we were able to isolate the mixture of protected vitamins **8**, albeit in low yield (20 %). Note that the use of additives such as CuI or ligands such as tris-(2-furyl)phosphine (TFP), which have recently been reported to accelerate the Stille coupling reaction, did not induce significant improvements.[9]



Scheme 2

Since the coupling reaction appeared to be mainly affected by the nature of the organometallic fragment, it was envisaged that use of an even less sterically demanding and more reactive derivative such as an organozinc halide[10] might give better results. To our delight, *room temperature* reaction of **6c** (prepared *in situ* from bromide **5**) with iodide **7** in the presence of 5 mol % $Pd(PPh_3)_4$ gave the expected mixture of protected 1α– and 1β-hydroxy-3-deoxyvitamin D_3 derivatives **8** smoothly and in excellent yield (95 %). Interestingly, these diastereoisomers were easily separated by flash chromatography and deprotected by treatment with *n*-tetrabutylammonium fluoride in THF. The structures of **9a** and **9b** were corroborated by comparison of their ^1H NMR spectra with those of authentic specimens.[11, 12]

The coupling reaction was carried out according to the following procedure. A cooled (-78 °C) solution of bromide **5** (0.15 mmol) in Et_2O (1.5 ml) was treated with *t*-BuLi (0.37 mmol, 2.5 M in THF). After stirring for 15 min under argon, a solution of freshly dried $ZnBr_2$ (0.22 mmol) in THF (1 ml) was added, and the mixture was stirred for 1 h at -10 °C. A mixture of iodide **7** (0.10 mmol) and $Pd(PPh_3)_4$ (0.005 mmol, 5 mol %), previously stirred in THF (1 ml) under argon at room temperature for 15 min, was added to the newly cooled (-78 °C) solution obtained above. The cooling bath was removed and the mixture was stirred at room temperature for 2 h, whereupon it was quenched with aqueous ammonium chloride. Work up by standard procedures and flash chromatography (hexanes) of the residue afforded the desired compounds.

Table 1. Palladium-catalysed cross-coupling of **6** and **7**.[a]

M	Catalyst[b]	Solvent	Temp (°C)	Time[f]	**8** (% yield)
n-Bu_3Sn	$Cl_2Pd(CH_3CN)_2$	DMF	25	3 days	-
n-Bu_3Sn	$Cl_2Pd(CH_3CN)_2$	THF	60	1.5 day	-
n-Bu_3Sn	Pd_2dba_3/TFP[c]	NMP	25	3 day	-
Me_3Sn	$Cl_2Pd(CH_3CN)$	DMF	25	4 days	20
Me_3Sn	Pd_2dba_3/TFP[c]	NMP[e]	25	4 days	23
Me_3Sn	Pd_2dba_3/TFP[c]	NMP	50	2days	-
Me_3Sn	Pd_2dba_3/TFP/CuI[d]	DMF	25	4 days	33
BrZn	$Pd(PPh_3)_4$	THF-Et_2O	25	2 h	95

a. 1.5 equiv. of **6** were used. *b*. 5 mol %. *c*. 1:2 mole ratio. *d*. 1:4:4 mole ratio. *e*. N-methyl-pyrrolidinone. *f*. Until **6** disappeared (TLC and NMR monitoring).

Thus the reaction of A-ring iododienes with alkenylzinc reagents bearing the C,D ring/side chain portion, in the presence of a catalytic amount of a Pd-phosphine complex, provides a new, efficient entry to the vitamin D skeleton. Unlike other convergent approaches that require high temperatures to assemble the triene system,[8,13] the coupling reaction we use proceeds under mild conditions making this approach especially attractive for the preparation of thermally sensitive analogues of the hormone **1**, such as those with a modified triene moiety. Work on the preparation of such compounds is under way.

Acknowledgements. We thank the DGICYT (Grant SAF 92-0572, M.E.C., Spain) for financial support, and the Xunta de Galicia for a fellowship to A.M.G..

References and Notes

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11. ^{1}H NMR (250 MHz, CD_2Cl_2), **9a**: 6.27, 5.98 (2H, ABq, J =11.3 Hz), 5.24 (1H, t, J = 1.8 Hz), 4.88 (1H, t, J = 1.8 Hz), 4.04 (1H, m), 0.91 (3H, d, J = 6 Hz), 0.85 (6H, d, J = 6 Hz), 0.53 (3H, s). **9b**: 6.28, 5.98 (2H, ABq, J =11.3 Hz), 5.23 (1H, t, J = 1.7 Hz), 4.86 (1H, t, J = 1.7 Hz), 4.09 (1H, m), 0.90 (3H, d, J = 6 Hz), 0.85 (6H, d, J = 6 Hz), 0.52 (3H, s).

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(*Received in UK* 20 *April* 1995; *revised* 26 *May* 1995; *accepted* 2 *June* 1995)