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HIGHLY SELECTIVE SYNTHESIS OF VITAMIN A AND ITS DERIVATIVES. CRITICAL COMPARISON OF SOME KNOWN PALLADIUM-CATALYZED ALKENYL-ALKENYL COUPLING REACTIONS

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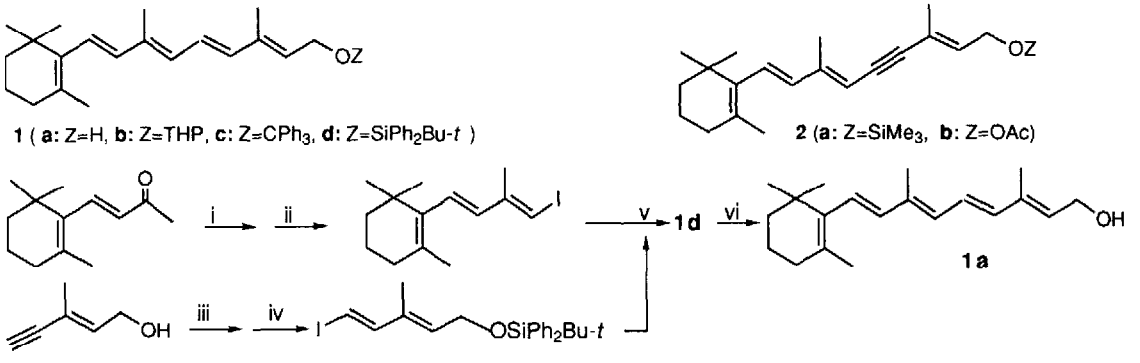
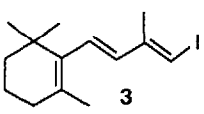
Summary: Vitamin A has been synthesized cleanly and selectively with essentially complete control of stereo- and regiochemistry in four linear and six overall steps from β-ionone and (*E*)-3-methyl-2-penten-4-yn-1-ol via Pd-catalyzed cross coupling of an alkenylzinc with an alkenyl iodide; the use of other metals, such as Al, Zr, Mg, B, Cu, and Sn, being inferior to that of Zn.

Synthesis of conjugated dienes via direct coupling of two alkenyl derivatives is an attractive synthetic strategy. Critically needed are those procedures that display high cross/homo coupling ratios and high stereo-, regio-, and chemoselectivities.[1] A Pd-catalyzed procedure involving alkenylalanes[2] introduced for the first time in 1976 provided satisfactory results with respect to the requirements specified above. Since then several related Pd-catalyzed procedures involving various metals, such as Zr,[3] Zn,[4] Mg,[5] B,[6] Cu,[7] and Sn,[8] have been reported. The great majority of the results available at present, however, pertain to the synthesis of sterically less demanding and functionally simple dienes.[9] Consequently, critical studies of the scope and limitations including comparison of the reported procedures are still lacking. In this study, we chose vitamin A (**1a**)[10] as a critical test case for probing the scope and limitations of known representative procedures. Herein we present a highly selective synthesis of vitamin A summarized in Scheme 1, which appears to represent the first application of the Pd-catalyzed alkenyl-alkenyl coupling to the synthesis of retinoids, and the results of comparison of various known procedures for Pd-catalyzed alkenyl-alkenyl coupling.



Scheme 1 i) 1. LDA,THF, 2. $ClPO(OEt)_2$, 3. LDA(2.2 x). ii) 1. Me_3Al, Cl_2ZrCp_2,CH_2Cl_2, I_2,THF. iii) 1. DIBAH(2x),hexane, 2. I_2 ,THF. iv) $ClSiPh_2Bu$-*t*, Et_3N, DMAP (1%), CH_2Cl_2. v) 1. *t*- BuLi (2x) , 2. $ZnBr_2$,THF , 3. $Pd(PPh_3)_4$ (4%) . vi) *n*-Bu_4NF , THF.



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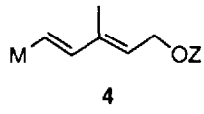

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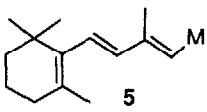
(**a:** M= $ZrCp_2Cl$, Z=THP , **b:** M= Z= $Al(Bu\text{-}i)_2$, **c:** M= Z= $ZrCp_2Cl$, **d:** M= Z= ZnBr , **e:** M=$ZrCp_2Cl$, Z=$SiPh_2Bu\text{-}t$)



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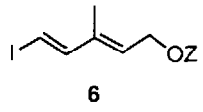
(**a:** M=$AlMe_2$, **b:** M=$Zn_{1/2}$, **c:** M=$Mg_{1/2}$)



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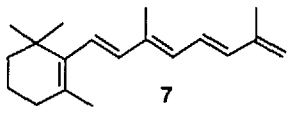
(**a:**Z=H, **b:**Z=$AlMe_2$, **c:**Z=THP , **d:**Z=CPh_3 , **e:** Z=$SiPh_2Bu\text{-}t$, **f:**Z=$SiMe_2Bu\text{-}t$, **g:** Z=Ac)



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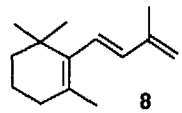

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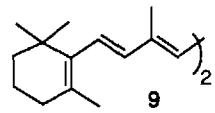

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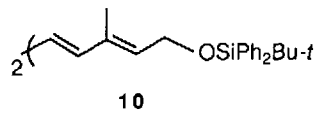

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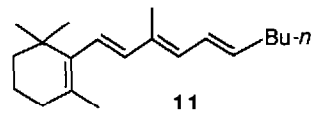

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We earlier synthesized selectively and in high yield 11,12-dehydrovitamin A derivatives **2a** and **2b** via Pd-catalyzed cross coupling, but their conversion into vitamin A and its derivatives via partial reduction was not performed in a highly selective manner.[11] Alternatively, the synthesis of vitamin A and its derivatives via cross coupling could be achieved by coupling either **3**[11,12] with **4** or **5** with **6**. In view of the sensitivity of vitamin A and its derivatives to various conditions, especially acidic, for deprotection of the OH group, we first considered the use of the unprotected derivatives of (*E,E*)-3-methyl-2,4-pentadien-1-ol, which were to be in situ converted to metal derivatives corresponding to alkenylmetal derivatives used as either **4** or **5**. Unfortunately, the Pd-catalyzed reaction of **3** with **4b** or **4c**, generated via the corresponding hydrometallation of (*E*)-3-methyl-2-penten-4-yn-1-ol, did not produce vitamin A in detectable amounts. Equally disappointing were the use of **4d**, generated in situ via sequential treatment of (*E,E*)-3-methyl-5-iodo-2,4-pentadien-1-ol (**6a**) with *t*-BuLi (3 equiv) and $ZnBr_2$ (2 equiv) as well as the Pd-catalyzed reaction of **5a**[11-13] with **6b**, generated by treatment of **6a** with Me_3Al. Since both the reaction of **3** with (*E*)-3-methyl-1,3-butadienylmetals containing ZnBr or $ZrCp_2Cl$ and that of **5b** with (*E*)-4-iodo-2-methyl-1,3-butadiene proceeded smoothly in the presence of 4 mol % of $Pd(PPh_3)_4$ to give the expected pentaene **7** in 70-100% yields, the difficulty encountered above was judged to pertain to the terminal oxy functionality. It thus became essential to find an appropriate protecting group which not only permits clean deprotection to give vitamin A in the final step but also is compatible with Pd-catalyzed cross coupling.

Accordingly, we prepared **6c-6e** as >98% isomerically pure compounds following the usual procedures for protection.[13] The compound **6f** decomposed during the isolation process, and **6g** was unstable and obtained only as a 4:1 (*E,E*)- and (*E,Z*)-isomers unsuitable for a stereoselective synthesis of vitamin A. By far the most stable derivative was **6e**, which was crystalline (mp 77-78°C) and stable for at least several months in a freezer. The reaction of **5b** with **6c**, **6d**, and **6e** catalyzed by 4 mol % of $Pd(PPh_3)_4$ in THF produced the desired vitamin A derivatives **1b** (73%), **1c** (58%), and **1d** (87%, 70% isolated), respectively, in the NMR yields indicated in parentheses. The reaction with **6d** was not very clean, producing **8** (17%) and deiodinated **6d** (8%) as well as the unreacted **6d** (17%) in the amounts indicated in

parentheses. On the other hand, the other two cases, especially that with **6e**, were clean, the amount of each byproduct or the starting compounds being < 5% Although all our attempts to convert **1b** and **1c** into vitamin A via deprotection were unsuccessful, treatment of **1d** with $(n\text{-Bu})_4NF$ in THF cleanly produced vitamin A in 84% yield. The isomeric purity of the crudely isolated vitamin A was ≥ 98%, as judged by ^1H and ^{13}C NMR spectroscopy and HPLC. In summing up, β-ionone was converted to **3** in two steps in 64% overall yield, and **6e** was prepared from commercially available (*E*)-3-methyl-2-penten-4-yn-1-ol in two steps in 40% overall yield. In the two additional steps described above, i.e., in four linear steps, vitamin A was obtained in 38% yield based on β-ionone. Particularly noteworthy is that all of the steps proceeded with essentially complete control of stereo- and regiochemistry. The present method appears to be the only example of nearly 100% stereoselective synthesis of vitamin A, where the stereochemistry is *reagent-controlled*, all the other known methods employing olefin-forming reactions the stereoselectivity of which is *substrate-dependent*, irrespective of the reported results.[10]

Table 1. The Preparation of a Silyl Derivative of Vitamin A via Pd-Catalyzed Alkenyl-Alkenyl Coupling[a]

Metal group in **5**	Solvent	Time h	Temp. °C	Yield or amount, %[b] **1d**	**9**	**10**	**6e**
$ZnI_{1/2}$[c]	THF	1	25	87	4	trace	0
$AlMe_2$[d]	THF	3	25	41	5	3	33
$AlMe_2$ (+ $ZnCl_2$, LiCl)[e]	THF, DMSO	3	25	60	*f*	*f*	13
$MgI_{1/2}$[c]	THF	3	25	57	2	1	35
$SnMe_3$[d]	THF or HMPA	3	25	trace	trace	trace	≥90
$SnMe_3$[d]	HMPA	3	65	39	18	19	trace
$Cu{\cdot}MgX_2$[g]	THF	3	-20 to 25	11	10	8	64
$BO_2C_6H_4$[d] (+ NaOMe)	benzene, MeOH	3	reflux	trace	*f*	*f*	14
$ZrCp_2Cl$[d]	THF	6	25	trace	33	17	67

[a]Unless otherwise mentioned, the reaction of **6e** with 1.1 equiv (based on **3**) of **5** was carried out in the presence of 4 mol % of $Pd(PPh_3)_4$. [b]By ^1H NMR. [c]Prepared by in situ treatment of **3** with 2 equiv of *t*-BuLi (-78°C) and 0.5 equiv of $ZnBr_2$ or $MgCl_2$ (-78 to 25°C). [d]Prepared by lithiation of **3** as above followed by addition of $ClAlMe_2$, $ClSnMe_3$, *B*-bromocatecholborane, or Cp_2ZrCl_2. [e]Via in situ carboalumination in the presence of 1 equiv of Cp_2ZrCl_2 followed by addition of 1 equiv each of $ZnCl_2$ and LiCl. The catalyst used was generated by treating dichlorobis[tris(2-furyl)phosphine]palladium with 2 equiv of *n*-BuLi. [f]Not possible to determine by ^1H NMR. [g]Prepared by sequential treatment of **3** with Mg in THF (60°C, 2 h) and $CuBr_2{\cdot}SMe_2$ (-30°C, 0.5 h).

With the goals of (i) further optimizing the synthesis of vitamin A and (ii) critically comparing various known Pd-catalyzed alkenyl-alkenyl coupling procedures,[3-8] we screened seven metals mentioned earlier. One specific goal was to be able to generate in situ an alkenylmetal derivative and use it directly in the Pd-catalyzed cross coupling. Accordingly, the reactions of **5** with **6e** in the presence of 4 mol % of $Pd(PPh_3)_4$ were carried out using the conditions optimized in previous studies,[3-8] and the results are summarized in Table 1. The use of **5a**, generated in situ via Zr-catalyzed carboalumination,[12] in conjunction with $Pd(PPh_3)_4$ and $ZnCl_2$ in THF[4] gave disappointing results which were not fully analyzed. A modified procedure using tris(2-furyl)phosphine[15] in place of PPh_3 and DMSO as a cosolvent did

produce vitamin A in 60% yield (^{1}H NMR). However, a delicate chromatographic separation was required for obtaining pure vitamin A. The use of the Mg reagent **5c** led to similar results that were less satisfactory than those obtained with the Zn reagent. Lower product yields and extensive homo-coupling reactions to give **9** and **10** were observed with Sn, Cu, and Zr. In contrast, a disubstituted alkene reagent **4e**, generated in situ via hydrozirconation, reacted with **3** in THF-DMSO at 25°C in the presence of 3 mol % of a catalyst, generated in situ by treating dichlorobis[tris(2-furyl)phosphine]palladium with 2 equiv of *n*-BuLi, provided **1d** in 52% NMR yield, with 31% of **3** remaining unreacted. The difficulty observed with B may well be chemoselective in nature, since the same catecholborane derivative prepared in situ from **3** nicely coupled with (*E*)-1-iodo-1-hexene under the same conditions to give **11** in 68% yield.

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