Tetrahedron Letters, Vol. 34, No. 19, pp. 3079-3082, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Convergent Approaches to the Vitamin D Skeleton Using a Transition Metal Catalyzed Carbometalation/Capture Strategy

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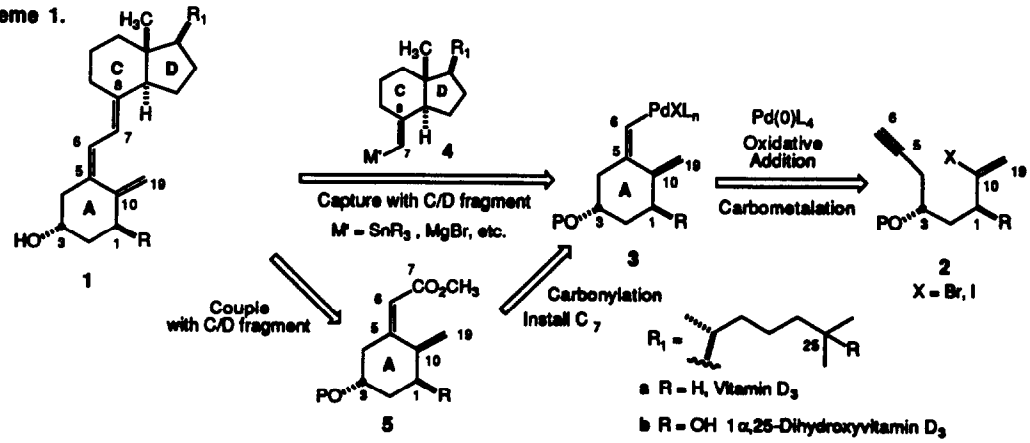
Abstract : Two concise, highly convergent strategies for the synthesis of Vitamin D derivatives are presented. Beginning with synthons of exceedingly low complexity, each approach utilizes a transition metal catalyzed intramolecular carbometalation for the stereoselective formation of the critical (bis)exocyclic diene subunit.

1α,25-Dihydroxyvitamin D_3 (**1b**), the hormonally active form of Vitamin D_3 (**1a**), possesses an exciting spectrum of pharmacological activity in addition to its traditional role in calcium homeostasis.[1] For example, this hormone has been shown to induce cellular differentiation[2] and inhibit cell proliferation,[3] thereby making it an attractive candidate for use in the treatment of cancers and various skin disorders.[2] Recent reports have also documented the immunosupressive properties of this hormone,[4] opening new avenues for the therapuetic uses of this agent and structural congeners. Although therapeutically effective doses of **1b** are known to induce hypercalcemia,[5] the significant potential of this agent has led to a resurgence of interest in the design and synthesis of analogues of **1b** retaining the therapeutic efficacy of this agent while exhibiting considerably diminished side effects.[6]

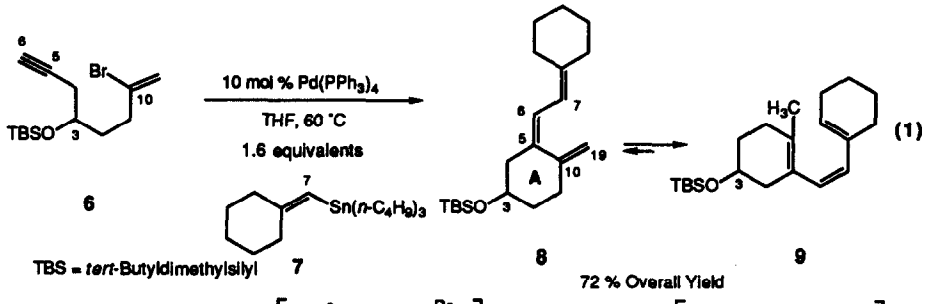
Several groups have recently described transition metal mediated strategies for the assembly of **1b** and related molecules;[7] these reports prompt us to disclose our initial results on the use of transition metal catalyzed carbometalation based strategies for the stereoselective construction of this important class of molecules. We have been exploring two alternate convergent strategies (Scheme 1), each utilizing a transition metal catalyzed carbometalation[8] reaction as the key step for the construction of the highly unsaturated trienyl portion of this molecule (C19-C8). In each case intramolecular carbometalation effects both formation of the key C10-C5 bond

Scheme 1.

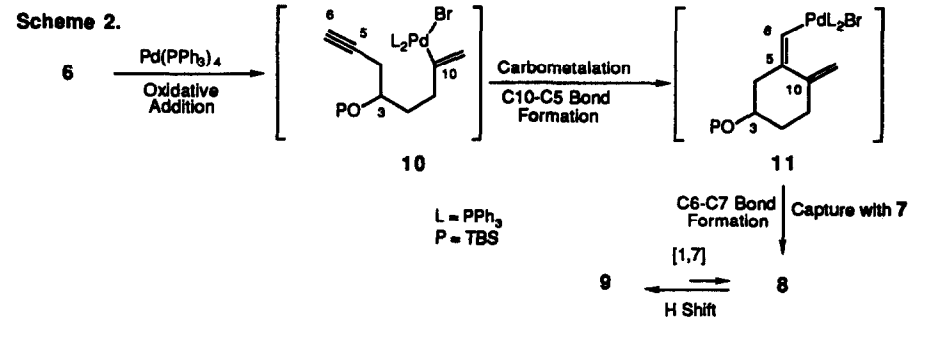


(and the A ring) and affords complete control over the exocyclic C5-C6 olefin geometry. Our initial "tricyclic" strategy is one that utilizes an intramolecular carbometalation for formation of the A ring and the (bis)exocyclic diene; the intermediate formed in this process (**3**) then is captured by an organometallic C/D fragment (in this case M = $SnBu_3$, though ZnCl, MgBr, and other metal derivatives, could, in principal, be used) in an intermolecular reaction reminescent of a Stille coupling.[9,10] This protocol should afford the hormone in one operation with total control over the critical triene geometry. A second strategy, which could prove very useful for the synthesis of analogues[6] of **1b**, captures intermediate **3** directly with carbon monoxide to afford a precursor to A ring synthon **5**.[11] This route is particularly atttractive for the facile synthesis of analogues of **1b** as the coupling of an A ring synthon with a C/D fragment in a Horner-Emmons reaction has proven a popular and effective strategy for the construction of these compounds.[12]

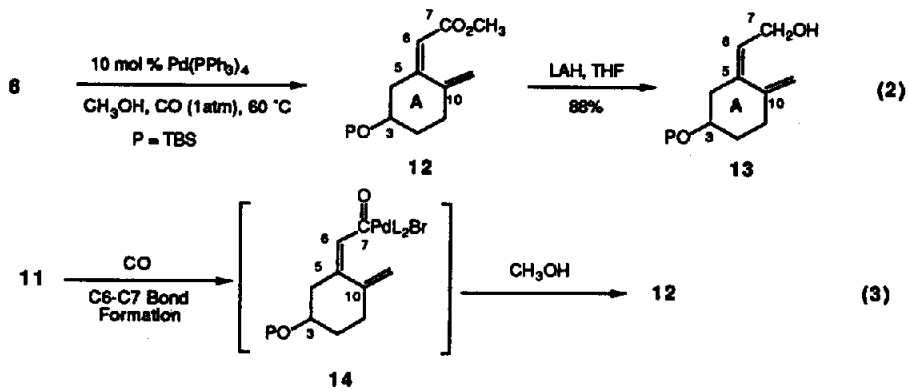
The implementation of the convergent "tricyclic" strategy in a model system is shown in Equation 1. Reaction of vinyl halide **6**[13] and 1.6 equivalents of the vinyl stannane **7**[14] (this fragment serves as a model for the C/D synthon neccessary for the production of Vitamin D systems, **4**) with 10 mol% $Pd(PPh_3)_4$ (60 °C, toluene, 0.03 M in **6**) affords a 72% yield of the mixture of **8** and **9**. The formation of these products can be rationalized by invoking an initial oxidative addition of the Pd(0) complex to the labile C10-Br bond of **6** (Scheme 2); this is followed by complexation of the pendant alkyne and *syn* carbometalation[8] (C10-C5 bond formation), giving the (bis)exocyclic dienyl metal **11**. Complete control over the C5-C6 olefin geometry is afforded by the required *syn* facial carbometalation.[8] Intermediate **11** then reacts rapidly with vinyl stannane **7** in a process similar to a Stille coupling,[10] affording triene **8**, which exists in a ca. 1 : 11 equilibrium with its [1,7] H shift isomer **9**.[15] No other C5-C6 olefin isomers are observed. Note that the intramolecular carbometalation is considerably more facile than direct reaction of the stannane **7** with the initially formed metal-carbon σ-bonded species **10**, as none of the direct coupling product is produced. This phenomena has been observed previously by us and others.[9] The product of this carbometalation/anion capture process **8** exists in a ca. 1 : 11 equilibrium favoring its "previtamin" isomer **9**.[15] The [1,7] H shift of trienes related to Vitamin D has been thoroughly described by Havinga and Okamura,[15] and is not expected to impede the implementation of this strategy for the synthesis of the tricyclic Vitamin D system.



Scheme 2.



Intramolecular carbometalation can also provide rapid access to A ring synthons necessary for implemenation of the "Lythgoe-Roche" A-C/D coupling strategy [12] for the synthesis of Vitamin D systems. This can be easily accomplished by trapping the dienylmetal intermediate produced upon intramolecular carbometalation (**11**) with carbon monoxide rather than the vinylstannane (**7**) used int he earlier approach; the requirement for *syn* facial carbometalation[8] controls the C5-C6 olefin geomtry and the carbonylation permits facile installation of the requisite functionality at C-7 neccessary for coupling to the C/D fragment. As shown in Equation 2, reaction of **6** with $Pd(PPh_3)_4$ (10 mol%) under an atmosphere of carbon monoxide in methanol cleanly affords dienoate **12** (78%). An explanation for this is shown in Equation 3. Intramolecular carbometalation of the intermediate **10** occurs more rapidly than direct carbonylation of this intermediate, as was seen with the capture by the tin reagent; reaction of **11** with CO then affords **14**, which, following methanolysis, leads to **12**. Dienoate **12** is a direct precursor of the A ring synthon utilized by Lythgoe[12a] in his convergent synthesis of Vitamin D_2. Esters similar to **12** have also been made in the calcitriol series by Posner.[16] Ester **12** can be efficiently reduced (LAH, Et_2O, 88%) to give **13**, which is identical in all respects (except optical rotation) with material derived directly from degradation of Vitamin D_2.[17] This strategy should prove useful for analogue synthesis due to the simplicity of the precursors required for this sequence of reactions, and should also allow simple installation of isotopic labels in derivatives of Vitamin D.



In conclusion, we have shown that transition metal catalyzed intramolecular carbometalation provides rapid access to the (bis)exocyclic diene moiety present of Vitamin D_3 and related compounds from synthons of exceedingly low complexity. The use of this strategy for the synthesis of **1** and **1a**, as well as analogues of this pharmacologically potent class of compounds, will be the subject of future reports.

Acknowledgements

The support of the University of California, Cancer Research Coordinating Committee and the National Institutes of Health (GM 46732-01) is gratefully acknowledged. MMH and BJM thank the Iranian Ministry of Culture and the Nathianel S. Coleman Undergraduate Research Fund (University of California, Riverside), respectively, for financial assistance.

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(Received in USA 9 February 1993)