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Pd(0)-Catalyzed-Mediated Synthesis of Vitamin D Compounds

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Dedicated to Miguel A. Pericàs on the occasion of his retirement.

Abstract: 1α,25-Dihydroxyvitamin D_3 (1,25D_3), the hormonally active form of vitamin D_3, regulates mineral homeostasis, cell growth, cell differentiation-proliferation, apoptosis, and immune responses. 1,25D_3 activates more than 229 genes associated with several diseases, including arthritis, diabetes and cancer, suggesting its implications in a broader range of biological functions than originally thought. Despite the wide range of biological activities, the clinical applications of 1,25D_3 have been limited due to its collateral hypercalcemic effects. This problem has boosted intense synthetic activity in the vitamin D area in the last decades aimed at the development of highly active and non-calcemic analogs for treatment of hyperproliferative diseases. This review covers the most useful synthetic approaches to 1,25D_3 analogs containing the natural vitamin D triene system with emphasis on the Pd(0)-catalyzed transformations involved in the formation of the vitamin D triene system and A-ring synthons.

Keywords: Vitamin D; Synthesis; Pd(0)-catalyzed cyclizations; Pd(0)-catalyzed couplings; A-Ring synthons; Heck-Suzuki/Miyaura-Negishi-Sonogashira-Stille

1. Introduction

The relationship between vitamin D and rickets has been known for more than a century.[1,2] The term vitamin D refers to both vitamin D_3 (cholecalciferol, **1)** and vitamin D_2 (ergocalciferol, **2**). Vitamin D_2 can be found in plant sources such as mushrooms and yeasts and fortified foods, such as milk, cereal, and fruit juices. Vitamin D_3 can be found in fatty fish sources, egg yorks, and liver, but the most important source is its production in the body when the skin is exposed to sunlight.[3] Vitamin D_3 supplements are available in capsules, oil and tablet forms. Both vitamin D_3 and vitamin D_2 are considered equipotent in man.[4] The action of sunlight on 7-dehydrocholesterol (**3**) in the skin induces an electrocyclic opening of the **B**-ring to give previtamin D_3 (**4**), which undergoes a thermal [1,7]-sigmatropic hydrogen shift leading to the secosteroid vitamin D_3 (**1**).[5,6] Therefore, vitamin D_3 is not a true vitamin, although it is still called as such for historical reasons.[1–3,7] Vitamin D_3 itself is not biologically active, and before eliciting its biological functions must be transported in the blood by the vitamin D binding protein (DBP) to the liver, where it is enzymatically hydroxylated at C-25 to produce 25-hydroxyvitamin D_3 [25(OH)D_3, **5**), which is the most abundant vitamin D metabolite in the body and its levels are used as indicators of several pathologies.[8,9] A second enzymatic hydroxylation at C-1 in the kidney produces 1α,25-dihydroxyvitamin D_3 (1,25D_3, calcitriol, **6**), which is the active form of vitamin D_3 and behaves as the steroid hormones stradiol, testosterone etc. As the result of other enzymatic oxidations several hydroxylated vitamin D_3 metabolites have also been identified, most of them as excretion products, and only a few as biologically active compounds.[10]

Antonio Mouriño was born in Folgoso, A Coruña, in 1948 and raised in Ordes, a town near Santiago de Compostela (Spain). After graduation in chemistry in 1972 at the University of Santiago de Compostela working with Professor Ignacio Ribas on the synthesis of decorticasine alkaloid, he moved to the University of Basque Country (Lejona), where he obtained his PhD in 1975 with Professors Luis Castedo and Rafael Suau on the synthesis of oxoaporphines and structure elucitadion of the alkaloid Pontevedrine. Afterwards he carried out research as a postdoctoral FPI and CCHN fellow with Professor William Okamura on the chemistry and biology of vitamin D. In 1979 he moved to University of Santiago de Compostela where he remained for 40 years. He was Head of the Department of Organic Chemistry for the period 1987–1989, and visiting professor at the University of California-Berkeley (Prof. Henry Rapoport), ETH-Zürich (Prof Dieter Seebach), University of Joseph Fourier-Grenoble (Prof. Jean-Louis Luche), Boston College (Prof. Ross Kelly), IGBMC-Illkirch (Prof. Dino Moras), University of California-Irvine (Prof. Larry Overman), and Rikkyo University-Tokyo (Prof. Hiroaki Tokiwa). Antonio Mouriño is currently an Emeritus Professor at the University of Santiago de Compostela with major research interests on design, synthesis and biological evaluation of vitamin D receptor ligands and design and synthesis of gold-nanoparticles for medical applications.

Prolonged UV irradiation on previtamin D_3 leads to tachysterol$_3$ (**7**) and lumisterol$_3$ (**8**) to regulate excessive vitamin D_3 production.[5]

The hormone 1,25D_3 interacts with the vitamin D nuclear receptor (VDR), a member of the nuclear receptor superfamily, to dimerize with the retinoid X receptor (RXR). The resulting heterodimer binds to the vitamin D response elements (VDREs) in target gene promoters and recruits coactivator proteins to induce a cascade of events including the regulation of mineral homeostasis, cell growth, cell differentiation-proliferation, apoptosis, and immune responses.[8,11] 1,25D_3 activates more than 229 genes associated with several diseases, including arthritis, diabetes and cancer, suggesting that this hormone might have an even broader range of biological functions than originally thought.[12] Despite the wide range of biological activities, the clinical applications of the hormone 1,25D_3 have been limited due to its collateral hypercalcemic effects.[13] This problem has sparked interest in the development of less hypercalcemic and more selective 1,25D_3 analogs for the treatment of hyperproliferative diseases.[14,15] Unfortunately, the mechanism underlying the dissociation of the antiproliferative effects from the calcemic effects, as well as the conformational requirements for selective biological functions, have not yet been established.[16–18] Examples of relevant synthesized compounds which find clinical applications include 1α,24*R*$(OH)_2D_3$ (tacalcitol), 22-oxa-1α,25$(OH)_2D_3$ (oxacalcitriol), and 22-ene-26,27-dehydro-1α,25$(OH)_2D_3$ (calcipotriol), which display low calcemic activity and are used for treatment of psoriasis, and 2β-3-(hydroxypropoxy)-1α,25$(OH)_2D_3$ (eldecalcitol) that is marketed for treatment of osteoporosis.[13–15,19,20]

2. General Synthetic Approaches to Vitamin D Metabolites and Analogs

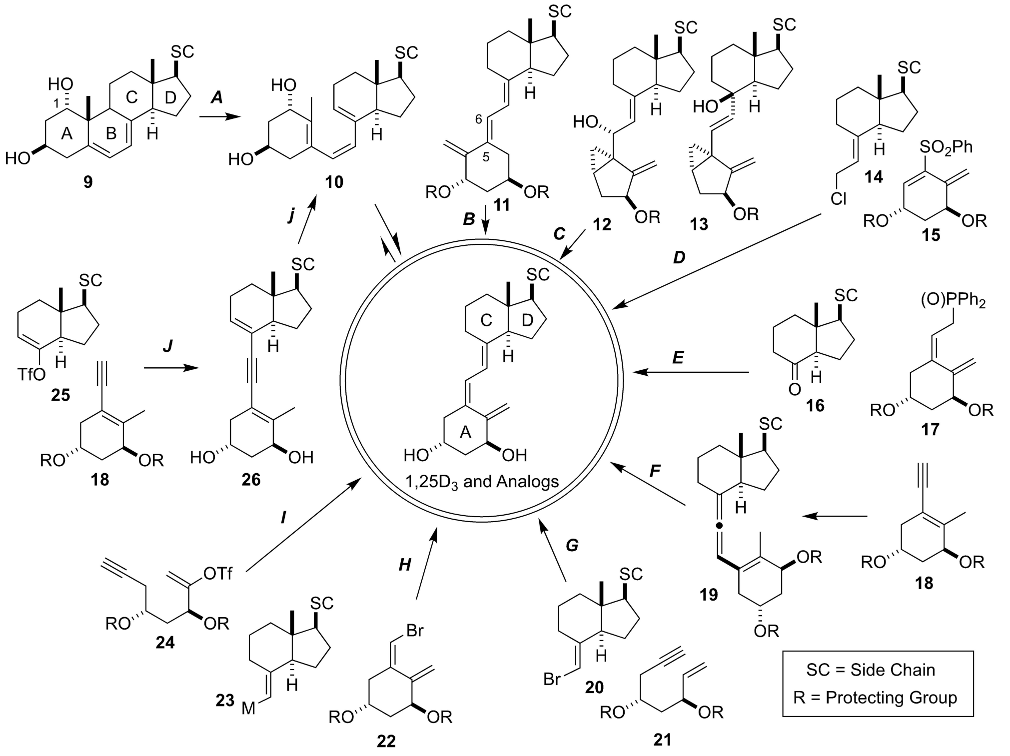
The potential therapeutic applicability of the hormone 1,25D_3 and its analogs in the treatment of various cancers and other proliferative diseases has led to an intense synthetic activity in the area in the last decades aimed at the development of highly active 1,25D_3-analogs with low or no calcemic action in comparison with the natural hormone. Some of these analogs have already been subjected to clinical trials.[13–15] Scheme 1 summarizes the selected ten general synthetic approaches *A–J* used to synthetize vitamin D analogs and metabolites. These synthetic approaches to vitamin D have been described in excellent reviews.[21–29]

3. The Classical Approach (*A*)

The Classical Approach (*A*) mimics the natural biogenetic pathway to vitamin D_3 and involves the photochemical B-ring opening of 7-dehydrocholesterol (**3**, Figure 1) leading to previtamin D_3 (**4**), which equilibrates to the vitamin D_3 form through a thermal antarafacial [1,7]-H shift.[30] This linear route is not recommended for the preparation of vitamin D metabolites and analogs due to several drawbacks including the multi-step introduction of the 1-OH group into the steroidal A-ring and the low yielding photochemical opening of the B-ring of provitamin D **9**.[31]

4. The Linear 5,6-trans-Strategy (*B*)

The Linear 5,6-trans-Strategy (*B*) involves the synthesis of vitamin D derivatives through stable 5,6-trans-vitamin D intermediates 11, which can be easily transformed into the corresponding vitamin D derivatives by photochemistry or iodine-catalyzed olefin isomerization.[32]



Scheme 1. Summary of the major approaches to 1α,25-dihydroxyvitamin D_3 metabolites and analogs.

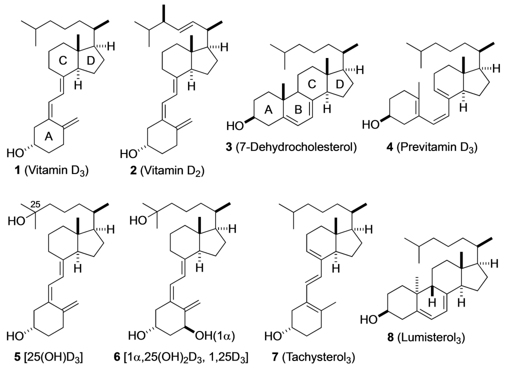


Figure 1. Structures of vitamin D_3 (**1**), Vitamin D_2 (**2**), 7-dehydrocholesterol (**3**), previtamin D_3 (**4**), 25-hydroxyvitamin D_3 (**5**), 1α,25-dihydroxyvitamin D_3 (**6**), tachysterol D_3 (**7**), and lumisterol D_3 (**8**).

5. The Cyclovitamin Approach (*C*)

The Cyclovitamin Approach (*C*) was originally developed by Mazur[33] and later improved by Schnoes and DeLuca,[34] Kametani,[35] Wilson,[36] and the Hoffman-La Roche group (Nutley).[37] This approach is based on the solvolitic rearrangements of cyclopropyl alcohols of type **12** or **13** to form the vitamin D triene system.[38]

6. The Convergent Approach via Sulfone (*D*)

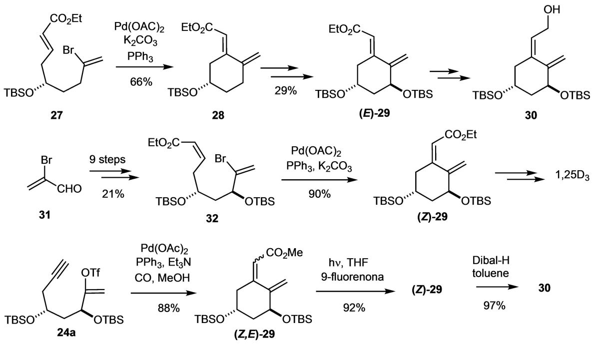
The Convergent Approach via Sulfone (*D*) features formation of the vitamin D triene system by coupling allylic intermediates of type **14** with A-ring–containing sulfones of type **15**. This new route was developed by Fuchs and is suitable for the synthesis of $1{,}25D_3$ analogs with modified A-ring.[39]

7. The Convergent Wittig-Horner Approach (*E*)

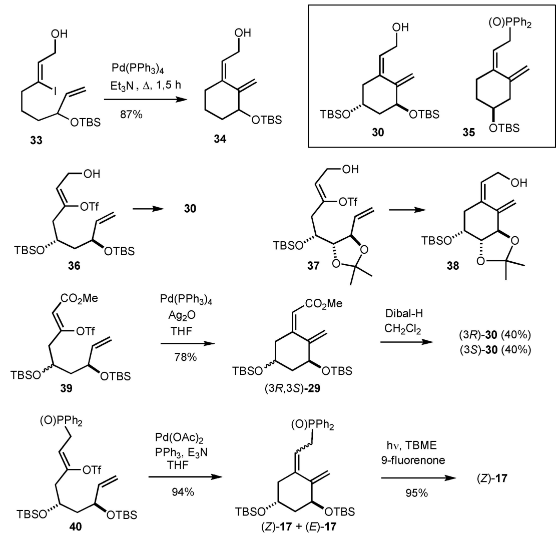
The Convergent Wittig-Horner Approach (*E*) developed by Lythgoe[21] and improved by the Hoffman-La Roche group (Nutley),[40] features direct formation of the vitamin D triene system by coupling the lithium anion of phosphine oxide **17** (A-ring) to a Grundmann's type ketone **16** (CD-side chain fragment) under mild conditions. The most useful CD-fragment is the Inhoffen-Lythgoe diol that can be prepared by degradation of vitamin D_2,[41] although related and versatile bicyclic CD-fragments have been obtained by total synthesis.[42] The commercial availability of phosphine oxide **17** makes this approach the method of choice to synthesize $1{,}25D_3$-analogs modified at the side chain. However, this approach suffers a few limitations namely: (a) direct coupling to prepare small amounts of up to 50 mg of vitamin D analog requires the use of an excess of the phosphine oxide **17**; (b) low yield obtained in the formation of the triene unit with alkylketones substituted at C11;[43] (b) unsuitable for the synthesis of analogs of 1,25D_3 with alkyl substituents at C-6[43] or aromatic D-ring;[44,45] (c) long multistep synthesis of phosphine oxides modified at the A-ring.[46]

The first example of palladium-catalyzed cyclization to vitamin D A-ring synthons for the Wittig-Horner approach was carried out in Shimizu's laboratory (Scheme 2).[47] Treatment of alkenyl bromide **27** with palladium acetate in the presence of triphenylphosphine and potassium carbonate afforded via reductive Heck-type cyclization the (*E*)-ester **28** in 66% yield. Compound **28** was then converted in several steps to allylic alcohol **30**, precursor of phosphine oxide **17**. The same laboratory synthesized the hormone 1,25D_3 starting from α-acrolein (**31**) using the Pd-catalyzed cyclization on bromide **32** as the key step to provide the ester *(Z)*-**29** in good yield.[48] Mouriño's laboratory used the same strategy to synthesize (*Z,E*)-**29** by Pd-catalyzed cyclization of enol-triflate **24a** and concomitant trapping of the resulting Pd(II)–intermediate with carbon monoxide in methanol. The mixture of esters (*Z,E*)-**29** was photochemically isomerized to ester (*Z*)-**29**, which was converted to phosphine oxide **17** by standard procedures.[49]

As a model for the stereoselective synthesis of A-ring-phosphine oxide precursors of 1,25D_3 analogs by the Wittig-Horner approach, Mouriño's group applied an intramolecular reductive Heck-cyclization process to generate allylic alcohol **34** from (*Z*)-alkenyliodide **33** (Scheme 3).[50] This strategy was later used for the preparation of allylic alcohol **30**, precursor of phosphine oxide **17**,[51–53] and phosphine oxide **35**.[54] Takahashi using enol-triflates instead of alkenyl iodides synthesized allylic alcohols **30**[55] and **38**[56] from **36** and **37**, respectively. Kubodera's group used the Pd-catalyzed cyclization of enol-triflates **39** in the presence of silver oxide to produce a mixture of esters (3*S*,3*R*)-**29**, which was reduced to a chromatographically separable mixture of alcohols (3*R*)-**30** and (3*S*)-**30**.[57] Hatakeyama's group under the Pd-catalyzed standard conditions converted enol-triflate **40** to a mixture of phosphine oxides (*Z*)-**17** and (*E*)-**17**, which was photochemically transformed into the desired isomer (*Z*)-**17** in high yield.[58]



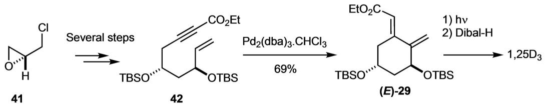
Scheme 2. Pd-catalyzed intramolecular reductive Heck-cyclization approach to vitamin D–A-ring synthons from vinyl bromides and viny triflates.



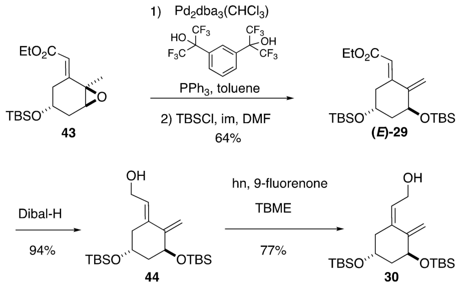
Scheme 3. Pd-catalyzed intramolecular reductive Heck-cyclization approach to vitamin D–A-ring synthons from internal alkenyl bromides and alkenyl triflates.

Ogasawara carried out a reductive Heck-cyclization of enyne **42** to generate ester (*E*)-**29** in good yield, which was then transformed into the hormone 1,25D_3 by standard methods (Scheme 4).[59,60]

Palladium-catalyzed opening of allylic epoxides was used by the Hoffmann-La Roche group (Nutley) to synthesize allylic alcohol **30** from epoxide **43**. Treatment of epoxide **43** with catalytic tris(dibenzylideneacetone)dipalladium(0) chloroform complex in the presence of a selected fluorinated alcohol as the proton source provided, after protection and reduction, the allylic alcohol **44**, which was photochemically isomerized to allylic alcohol **30** (Scheme 5).[61]



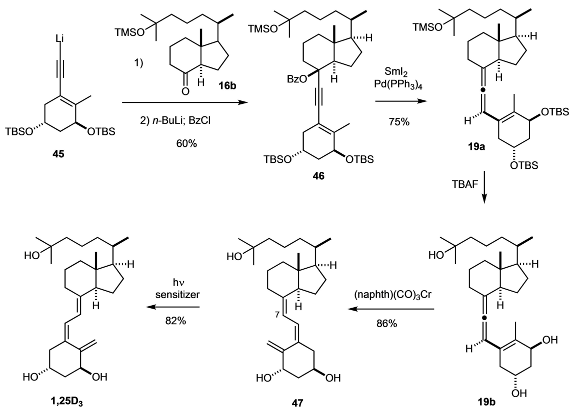
Scheme 4. Pd-catalyzed intramolecular reductive Heck-cyclization approach to vitamin D–A-ring synthons from enynes.



Scheme 5. Hoffmann-La Roche Pd-π-allyl route to vitamin D–A-ring synthons.

8. The Vinylallene Approach (*F*)

The Vinylallene Approach (*F*) was developed in Okamura's laboratory at Riverside.[62,63] The thermal isomerization of vinylallenes of type **19** (Scheme 1), leads to the natural vitamin D triene system or unnatural (7*Z*)-triene via sigmatropic [1,5]-H-shifts. This route has proven useful for the preparation of 1,25D$_3$-analogs with unsaturation at C-9,[64] modified A-ring,[26] and (7*Z*)-unnatural triene systems.[26] Scheme 6 illustrates the synthesis of the natural hormone 1,25D$_3$ as an example of this convergent route.[65] Coupling of **45** with ketone **16b**, followed by benzoylation of the resulting propargylic alcohol provided benzoate **46**. A solution of **46** and catalytic Pd(PPh$_3$)$_4$ in THF and 2-propanol were successively added to a solution of SmI$_2$ in THF to give, via formal anti-*S$_N$2'*-displacement of the benzoate group by hydrogen, vinylallene **19a** as the major product, which was deprotected to triol **19b**. Chromium(0)-mediated isomerization of **19b** gave the unnatural (7*Z*)-1α,25D$_3$ (**47**), which was photoisomerized to the natural hormone 1,25D$_3$.

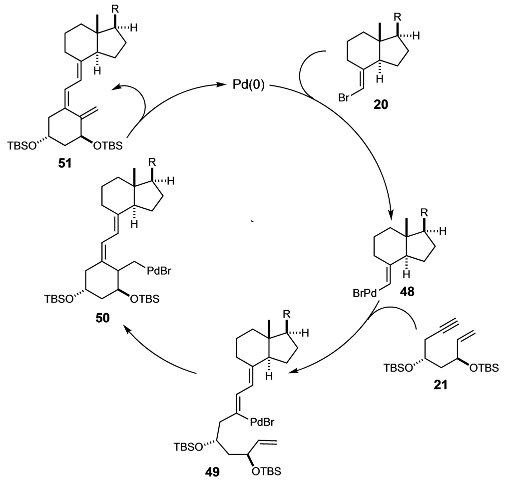


Scheme 6. Okamura's vinylallene approach to hormone 1α,25-dihydroxyvitamin D$_3$.

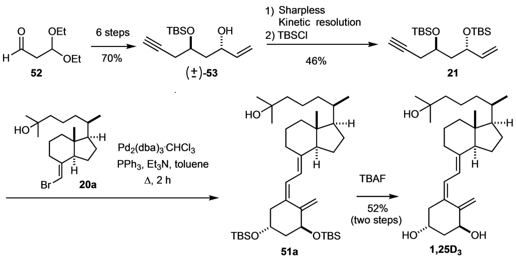
9. The Pd(0)-Catalyzed Alkylative-Cyclization Approach (*G*)

The Pd(0)-Catalyzed Alkylative-Cyclization Approach (*G*) (Scheme 1) developed in Trost's laboratory, involves Pd(0)-catalyzed coupling of A-ring enyne **21** with vinyl bromide **20** (CD-side chain fragment) to generate in a single step the vitamin D triene system.[66,67] Mechanistically, the process involves insertion of Pd(0)-species into bromide **20** to produce the Pd(II)-species of type **48** that undergoe *syn*-addition to the triple bond of enyne **21** leading to Pd(II)-intermediate **49**, which undergoes an intramolecular olefin insertion to produce intermediate **50**, which, after reductive elimination, gives the desired protected vitamin D analog **51** and HPdBr that regenerates the starting Pd(0)-species (Scheme 7). An important step in Trost route is the stereoselective preparation of (*E*)-alkenyl bromide **20** from the corresponding Grundmann's type ketone by Wittig bromomethylation.

Scheme 8 depicts Trost's approach to the hormone 1α,25-dihydroxyvitamin D$_3$.[67] Acetal **52** was converted to racemic enyne **53** in 70% yield (6 steps).



Scheme 7. Trost Pd(0)-catalyzed alkylative-cyclization mechanism

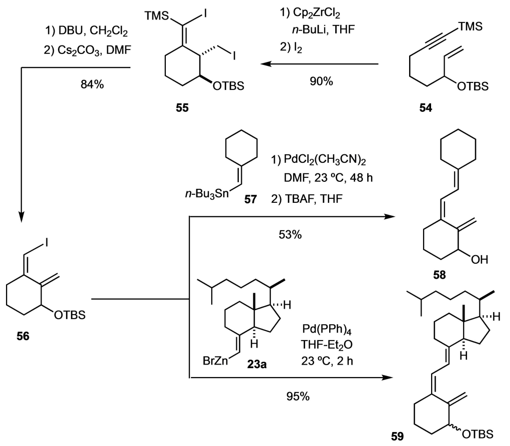


Scheme 8. Trost's synthesis of the hormone 1α,25-dihydroxyvitamin D$_3$

Sharpless kinetic resolution of enyne **53** and protection provided enyne **21** in 46% yield. A mixture of enyne **21** and vinyl bromide **20a** in toluene-Et_3N was heated at reflux to give, after work up and deprotection, the natural hormone $1,25D_3$ (17% overall yield). The synthesis of several $1,25D_3$ analogs in recent years by Trost's method makes it one of the synthetic routes of choice for the preparation of new $1,25D_3$ analogs. The relevance of this short pathway to $1,25D_3$ analogs has been demonstrated by the intense synthetic activity used for the preparation of substituted A-ring-enyne synthons[68–69] and vitamin D analogs modified at the A-ring.[70–80] The relative high temperature (reflux in triethyl amine-toluene) required for the Pd(0)-catalyzed alkylative cyclization is unsuitable for the formation of vitamin D analogs that undergo thermal equilibration to the previtamin D form such as 6-methyl-25-hydroxyvitamin D_3,[43,81] and aromatic-D-ring analogs.[44,45]

10. The Pd(0)-Catalyzed Cross Coupling Approach (*H*)

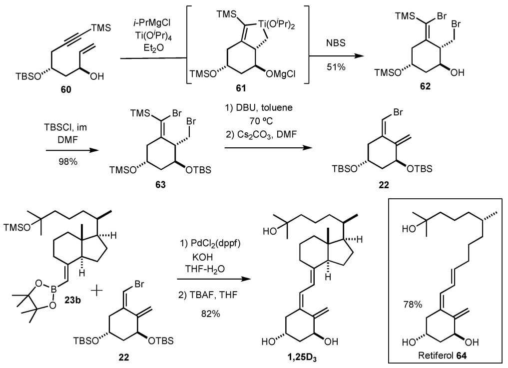
The Pd(0)-catalyzed cross coupling approach (*H*) to the vitamin D triene system was developed in Mouriño's laboratory in 1992.[82] As a model, the Stille version of this approach was examined by cross coupling between alkenyl iodide **56** and stannyl derivative **57** using $PdCl_2(CH_3CN)_2$ as the catalyst leading to triene **58** (Scheme 9). Negishi cross coupling between iodide **56** and alkenyl zinc bromide **23a** in the presence of catalytic $Pd(PPh_3)_4$ proceeded smoothly at room temperature to give a mixture of chromatographically separable diastereoisomers **59** in 95% yield.[83] This procedure was later used in the same laboratory for the construction of 3-deoxy-1-hydroxy-6-methyl-vitamin D_3 analogs demonstrating its applicability in the synthesis of thermally labile 1-hydroxy-vitamin D analogs.[84]



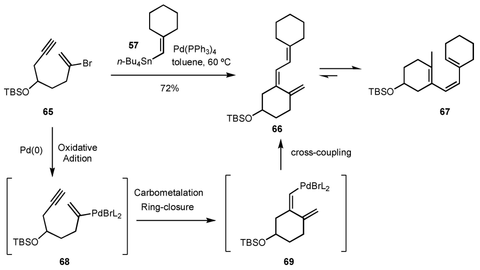
Scheme 9. Stille and Negishi cross-couplings to vitamin D triene system

Following a similar strategy, Sato and coworkers used a Suzuki-Miyaura coupling between A-ring-alkenyl bromides and CD-side chain-boronates to form the vitamin D triene system under mild conditions. This method was efficiently employed for the synthesis of the hormone $1,25D_3$ and its analogs including retiferols of type **64** (Scheme 10).[85–87] Sato's synthesis of $1,25D_3$ uses enyne **60**, which was converted via titanium intermediate **61** to alcohol **62**. Protection, bromide elimination and desilylation afforded diene **22**, which was coupled to boronate **23b** in the presence of catalytic $PdCl_2(dppf)$ and KOH in aqueous-THF to give, after deprotection, the natural hormone $1,25D_3$ in 82% yield.

In 1993, Nuss and coworkers at Riverside reported a Pd(0)-catalyzed process for the one pot generation of triene system **66** related to vitamin D using enyne **65** and vinyl stannane **57** (Scheme 11).[88] The formation of **66** was rationalized by an initial oxidative addition of Pd(0)-species to the C–Br bond, followed by *syn* carbocyclization of the resulting intermediate **68** to form intermediate **69**, which undergoes a Stille-cross coupling leading to triene **66**, which equilibrates at 60 °C by a sigmatropic [1,7]-H shift to the previtamin



Scheme 10. Sato's cross-coupling approach to the natural hormone $1,25D_3$ and analogs

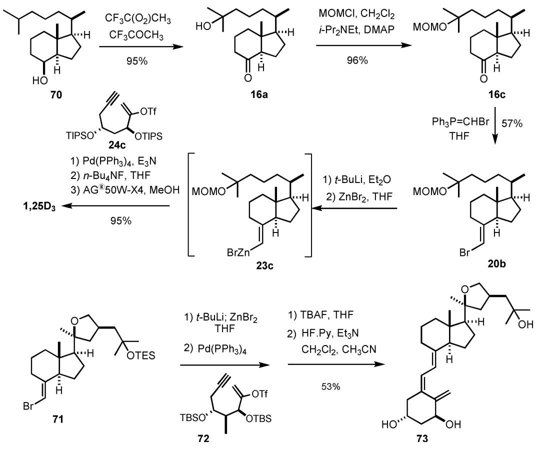


Scheme 11. Nuss' Pd(0)-catalyzed tandem ring-closure/Stille coupling to trienes related to vitamin D.

D like form **67**. The intramolecular cyclization was much faster than direct Stille coupling.

11. The Pd-Catalyzed Tandem Carbocyclization/Cross Coupling Approach (*I*)

The Pd-Catalyzed Tandem Carbocyclization/Cross Coupling Approach (*I*) involves an alkenyl-metal intermediate of type **23** (Scheme 1), enol-triflate **24**, and catalytic Pd(0)-species to generate the vitamin D triene system in one pot process under mild conditions. Based on the successful direct Stille and Negishi couplings[82–84] and tandem carbocyclizacion/Stille coupling approaches[88] to generate the vitamin D triene system in model systems, Mouriño's group developed an efficient procedure for the one pot construction of the vitamin D triene system by Pd(0)-catalyzed tandem ring-closure/Negishi coupling.[89] This efficient approach is exemplified by the synthesis of the natural hormone 1,25D$_3$ and vitamin D receptor superagonist **73** depicted in Scheme 12.[89,90] Alcohol **70** was obtained by degradation of vitamin D$_3$. Exposure of **70** to methyl(trifluoromethyl)dioxirane furnished directly 25-hydroxy-Grundmann's ketone (**16a**). Protection of **16a** as the methoxymethyl ether followed by bromoolefination provided alkenyl bromide **20b**, which was subjected to sequential metalation and transmetalation to give organozinc **23c**, which upon treatment with vinyl-triflate **24c** in the presence of catalytic Pd(PPh$_3$)$_4$ gave, after deprotection, the hormone 1,25D$_3$ (46% yield from alcohol **70**). Metalation and transmetalation of alkenyl bromide **71** and treatment of the resulting alkenyl-zinc intermediate with vinyl-triflate **72** gave, after deprotection, the 1,25D$_3$-analog **73** (53%).

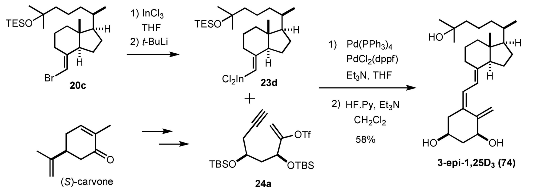


Scheme 12. Pd(0)-catalyzed tandem carbocyclization/Negishi cross-coupling approach to 1α,25-dihydroxyvitamina D$_3$ and VDR-superagonist **73**.

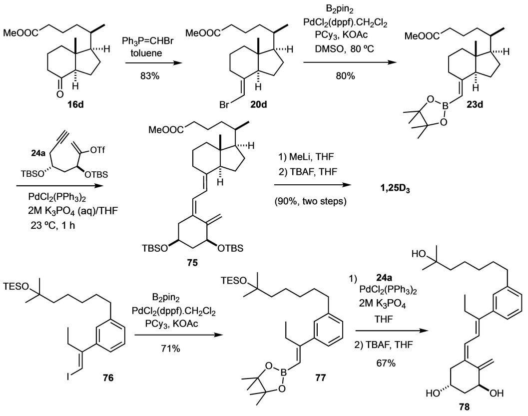
For reproducibility reasons, *alkenyl indium intermediate **23d** instead of the corresponding organozinc derivative* was used in the synthesis of 3-epi-1α,25-dihydroxyvitamin D$_3$ (an active vitamin D$_3$ metabolite) (Scheme 13).[91] Treatment of a mixture of alkenyl bromide **20c** and indium trichloride with *tert*-butyllithium and coupling of the resulting indium intermediate **23d** with enol-triflate **24a**, prepared in several steps from (*S*)-carvone, in the presence of catalytic amounts of Pd(PPh$_3$)$_4$ and PdCl$_2$(dppf) gave, after desilylation, the desired metabolite 3-epi-1,25D$_3$ (**74**) in 58% yield.

The palladium-catalyzed process for the construction of the vitamin D triene that couples enol–triflates with *alkenyl zinc or organoindium intermediates* was still limited by problems with reproducibility on the small-scale and required more than 1 equivalent of the upper (C/D) fragment under inert reaction conditions to afford moderate yields of the vitamin D analog.[89–91] 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, Mouriño and coworkers envisaged the possibility of employing alkenyl-boronic esters (**23**, M=B(OR)2; Scheme 1), instead of the corresponding alkenyl zinc or alkenyl indium intermediates of earlier work. A Suzuki-Miyaura coupling through palladium(II)-intermediate resulting from the initial cyclization of enol–triflate **24a**[50] provided the triene unit stereoselectively in one pot.[43] This *Pd-catalyzed ring-closure/Suzuki-Miyaura strategy* (Approach *I*, Scheme 1) indeed circumvents the problems associated with previous synthetic approaches providing a general method for the small-scale preparation of a wide variety of 1,25D$_3$ analogs in high yield, in protic medium, under mild conditions, in a practical, economical, and reproducible fashion, including 1,25D$_3$ analogs that show tendency to equilibrate with the corresponding previtamins or that cannot be obtained by the Wittig-Horner method.[44,45]

The scope of this approach is illustrated by the efficient construction of the triene moieties of the natural hormone 1,25D$_3$[43] and the highly active and non-calcemic analog **79**[92] (Scheme 14). Alkenyl bromide **20d** was prepared from ketone **16d** in 80% yield. Modified Miyaura's protocol on **16d** employing bis(pinacolato)diboron, potasium acetate, tricyclohex-



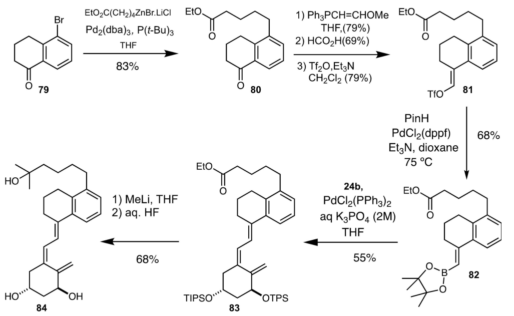
Scheme 13. Pd(0)-catalyzed carbocyclization/cross coupling with alkenyl-indium reagents.



Scheme 14. Pd(0)-catalyzed carbocyclization/Suzuki-Miyaura-mediated synthesis of the hormone 1,25D$_3$ and aromatic-D-ring analog **78**.

ylphosphine, and catalytic [1,1′-bis-(diphenylphosphino)ferrocene] dichloropalladium(II) in DMSO provided boronate **23d** in 80% yield. Treatment of a mixture of equimolar amounts of bororonate **23d** and vinyl-triflate **24a** in the presence of catalytic PdCl$_2$(PPh$_3$)$_2$ in aqueous 2 M K$_3$PO$_4$ in THF at 23 °C for 1 h delivered, after standard desilylation, the natural hormone 1,25D$_3$ in 90% yield. Using the same procedure, alkenyl iodide **76**, which was prepared from 3-bromobenzaldeyde (6 steps, 51% yield), was converted to aromatic-D-ring analog **78** (3 steps, 47%), (9 steps, 24% overall yield) (Scheme 14).

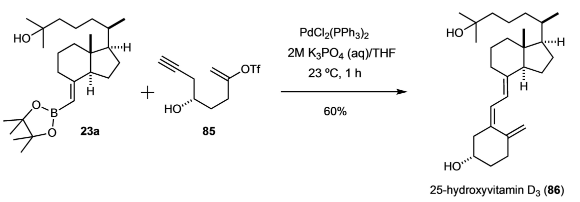
Another example that demonstrates the mildness of the cyclization/Suzuki-Miyaura approach is illustrated with the synthesis of aromatic-D-ring analog **84** (Scheme 15),[44] which could not be obtained by the Wittig–Horner approach ***E***, vinyallene route ***F***, or dienyne approach ***J***. Attempts to synthesized **84** by the tandem carbocyclization/Negishi method were unsuccessful due to Pd(0)-catalyzed homodimerization of the alkenyl Zn-intermediate. Pd(0)-catalyzed reaction of enol-triflate **81** with pinacolborane gave boronate **82** in 68% yield. In the key step, treatment of a THF solution of enol triflate **24b**, boronate **82** and aqueous K$_3$PO$_4$ (2 M) with a catalytic amount of bis-triphenylphosphine palladium (II) dichloride, afforded the desired vitamin D ester **83** in 55% yield. Methylation of **83** followed by deprotection afforded the desired analog **84** in 68% yield. Unexpectedly, this analog equilibrated largely to its previtamin D form on standing in CDCl$_3$ (ratio 1:2 after 120 h at room temperature).



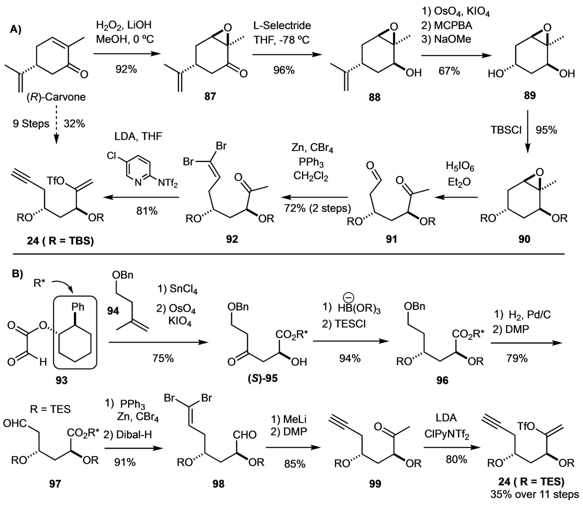
Scheme 15. Pd(0)-catalyzed-mediated synthesis of **84** by the cyclization/Suzuki-Miyaura approach.

The Pd(0)-catalyzed carbocyclization/Suzuki-Miyaura approach ***I***, has proven to be useful to synthesize several vitamin D$_3$ and 1,25D$_3$ analogs including the hormone 1,25D$_3$,[92–108] and 25-hydroxyvitamin D$_3$ (Scheme 16).[109] A drawback of the this approach is that the A-ring-enyne synthons **24a** and **85** are not commercially purchasable and must be prepared in the laboratory.

Two alternative approaches to the A-ring-enyne synthons **24** have been developed in Mouriño's group. The first approach[50] starts with the stereoselective epoxidation of (*R*)-carvone to give epoxide **87** (Scheme 17A). Reduction of **87** with L-Selectride® gave alcohol **88**, which was converted to diol **89** by the sequence: catalytic osmium tetroxide and potassium periodate; Baeyer-Villiger oxidation; and hydrolysis of the resulting acetate. Protection of **89** with TBSCl gave



Scheme 16. Pd(0)-catalyzed carbocyclization/Suzuki-Miyaura approach to 25-hydroxyvitamin D$_3$.



Scheme 17. Synthetic Approaches **A** and **B** to A-ring-enynes **24**.

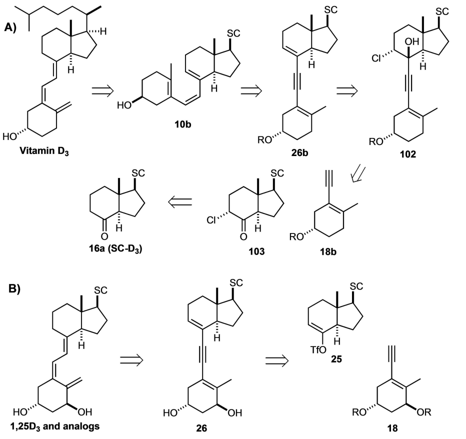
90, which was treated with periodic acid to give aldehyde **91**. Wittig reaction of **91** with $Ph_3P{=}CBr_2$ afforded vinylic dibromide **92**, which was converted to enol-triflate **24** (R=TBS) by treatment with LDA and trapping of the resulting enolate with by *N*-(5-chloro-2-pyridyl)triflimide.

A second approach to enyne **24**[110] starts with chiral glyosylate **93** (Scheme 17B). Treatment of a mixture of **93** and **94** with $SnCl_4$ and oxidative cleavage of the resulting olefin with catalytic osmium tetroxide in the presence of potassium periodate gave (*S*)-alcohol **95**. Evans reduction of **95** followed by protection and deprotective-hydrogenolysis afforded aldehyde **97**, which was subjected to chain extension with $Ph_3P{=}CBr_2$ and reduction of the resulting dibromide with Dibal-H to provide aldehyde **98**. Methylation of **98** followed by oxidation of the resulting alcohol with Dess-Martin periodinane afforded methyl ketone **99**. Finally, treatment of **99** with LDA followed by trapping of the resulting enolate with $ClPyNTf_2$ gave enyne **24** (R=TES).

A synthetic approach to A-ring-synthon **85**, required for the synthesis of 25-hydroxyvitamin D_3 metabolites and analogs was carried out in Mouriño's laboratory.[109] This approach is summarized in Scheme 18. Ozonolysis of (*S*)-(+)-limonene oxide followed by acetylation of the resulting hydroperoxide with Ac_2O and Criegee rearrangement of the resulting peroxyester provided, after protection, epoxide **100**. Periodic acid-oxidative cleavage of **100** and treatment of the resulting aldehyde with $Ph_3P{=}CBr_2$ gave vinyl dibromide **101**, which was transformed into the enol-triflate **85** by successive reactions with LDA, *n*-BuLi, trapping of the resulting enolate with $ClPyNTf_2$, and deprotection.

12. The Dienyne Approach (*J*)

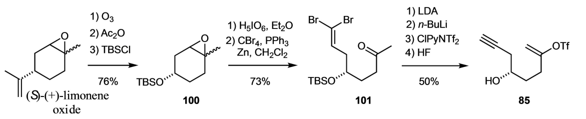
The Dienyne Approach (*J*) was reported in the early 1970's by Lythgoe and coworkers (Scheme 1).[111,112] In this approach, the previtamin D_3 (**10b**) (Scheme 19-A) was obtained by semihydrogenation of dienyne **26b** improving the low yielding photochemical **B**-ring opening of 7-DHC of the classical approach to vitamin D (**Approach *A***, Scheme 1). I drawback of Lythhoe's dienyne approach is the low yielding preparation of dienyne **26b** from Grundmann's ketone (**16a**) (about 7%). The substantial improvement introduced in Mouriño-Castedo laboratory in the preparation of 1α-hydroxylated dienyne **26** (Scheme 19B)[113–116] as well as the excellent synthesis of the A-ring enyne **18** by Okamura's group,[117,118] and more recently by Baran and coworkers,[42] makes the dienyne approach an attractive synthetic route to new $1,25D_3$ analogs according to the retrosynthesis depicted in Scheme 19-B.



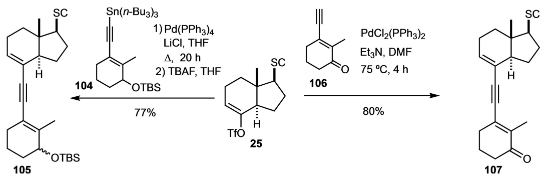
Scheme 19. A) Lythgoe's dienyne approach to vitamin D_3. B) Mouriño-Castedo Pd(0)-catalyzed improved approach to dienynes **26**.

The initial Pd(0)-catakyzed studies toward the synthesis of 1-hydroxy-dienynes as precursors of 1-hydroxy-vitamin D_3 derivatives started with enol-triflate **25** (SC-D_3), which was Stilled-coupled to stannyl enyne **104** using catalytic $Pd(PPh_3)_4$ in THF to give dienyne **105** in 77% yield (Scheme 20). The Sonogashira-coupling of **25** with enynone **106**, in the presence of catalytic $PdCl_2(PPh_3)_2$ in Et_3N-DMF, proceeded even faster to give dienynone **107** in higher yield (80%).[113,114] Therefore the Sonogashira-coupling was adopted to pursue the synthesis of 1α,25-dihydroxyvitamin D_3 and 1α,25-dhydroxyvitamin D_2 following the retrosynthetic analysis depicted in Scheme 19-B.[115,116]

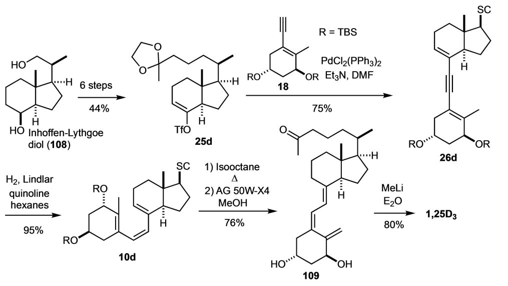
The synthesis of $1,25D_3$ through Sonogashira-route is outlined in Scheme 21.[116,117] Inhoffen-Lythgoe diol (**108**) was converted to enol-triflate **25d** (44% over 6 steps). Sonogashira-coupling of **25d** and enyne **18** in the presence of catalytic $PdCl_2(PPh_3)_2$ in Et_3N/DMF



Scheme 18. Synthetic approach to enol-triflate **85**, A-ring precursor of vitamin D_3 metabolites and analogs.



Scheme 20. Preliminary Stille and Sonogashira couplings to simple 1-oxygenated-dienynes

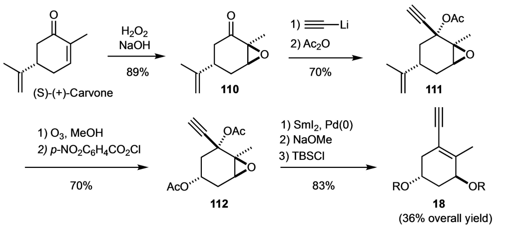


Scheme 21. Synthesis of $1,25D_3$ by the dienyne route ***J***.

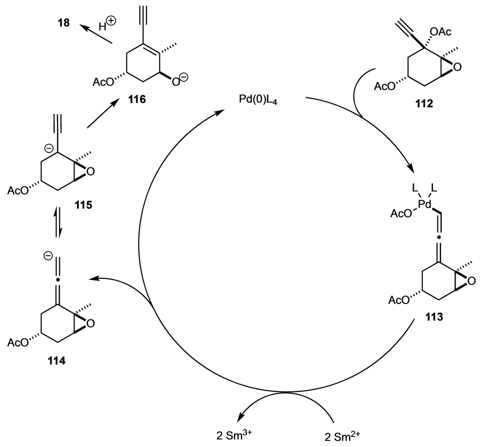
gave dienyne **26d** (75%), which was semihydrogenated in the presence of Lindlar catalyst and quinoline in hexanes to previtamin D_3 **10d** (95%). Thermal isomerization of **10d** in isooctane followed by deprotection gave the 25-keto-derivative **109** (76%), which was treated with MeLi in Et_2O to provide the hormone $1,25D_3$ (80%).

Scheme 22 summarizes the Okamura's efficient route to A-ring enyne **18**.[117,118] This practical 5-pot-synthesis of **18** (37% overall yield) involves selective epoxidation of (*S*)-(+)-carvone to produce epoxide **110** in high yield, which was successively treated with lithium acetylide and acetic anhydride to give propargylic acetate **111**. Side-chain degradation of **111** by reaction with ozone in MeOH and treatment of the resulting hydroperoxide intermediate with *p*-nitrobenzoyl chloride and Criegee rearrangement of the resulting methoxy peroxyester afforded diacetate **112** in 70% yield. In the key step, **112** was subjected to Pd(0)-SmI_2-promoted reductive elimination with concomitant epoxide ring opening to afford, after hydrolysis and protection, enyne **18** in 83% yield. Based on the mechanism proposed by Yamaguchi *et al.* for palladium-catalyzed reduction of propargylic acetates,[119] a plausible mechanism for this transformation is shown in Scheme 23. Alternative synthesis of A-ring enyne **18** have been described.[43,120–122]

The Dienyne strategy J has been successfully applied to the synthesis of several vitamin D metabolites and analogs.[43,111,112,116,123–141] This synthetic route has the following advantages: (1) the easy and short preparation of the A-ring-enyne synthons (bottom fragment); and (2) the easy preparation of the enol triflates (upper fragment) from the corresponding ketones. The main disadvantages are: (1) the overhydrogenation during Lindlar partial hydrogenation of the triple bond; (2) the low yield on vitamin D when thermal isomerization favors the previtamin D intermediate (for example 6-methyl-$1,25D_3$ analogs,[44] and aromatic-D-ring-$1,25D_3$ analogs;[45,46] and (3) the instability of the vitamin D compound under the thermal isomerization of the previtamin D form.



Scheme 22. Okamura's synthesis of A-ring enyne **18**.



Scheme 23. Proposed mechanism for the Pd(0)-catalyzed formation of enyne **18**.

13. Conclusion Remarks

The author reviewed the most used methods in the synthesis of metabolites of vitamin D and its analogs containing the natural vitamin D triene system, with special emphasis on the methodology and transformations catalyzed by palladium. In addition to the efficient Wittig-Horner Approach originally developed by Lythgoe in the 1970's, a few Pd(0)-catalyzed routes to vitamin D emerge as excellent or alternative methods for the rapid and mild construction of new $1,25D_3$ analogs. The Wittig-Horner Approach (***E***) appears to be the method of choice to synthesized $1,25D_3$ analogs modified at the side chain. The Pd(0)-Catalyzed Alkylative-Cyclization Approach (***G***) has proven to be useful to synthesize $1,25D_3$ analogs modified at the A-ring. The Pd(0)-Catalyzed Tandem Carbocyclization/Cross-Coupling Approach (***I***) has proven to be usefull for the preparation of small amounts of $1,25D_3$ analogs modified at the A-ring and triene system in protic medium. The Dienyne Approach (***J***) has been successfully used for the preparation of $1,25D_3$ analogs modified at the C-ring and previtamin D derivatives. The choice of the method to be used depends on the amount of analog to be prepared, the part of the vitamin D skeleton to be modified, and the availability of the A-ring-synthon. The author hopes that this review will be useful to chemists, biochemists, and biologists for the design of new vitamin D analogs of therapeutic potential as well as for the development of chemistry in general.

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