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Synthesis of Vitamin D_3 Triene System by using Pd-Catalyzed Cyclization of Dienol Triflate

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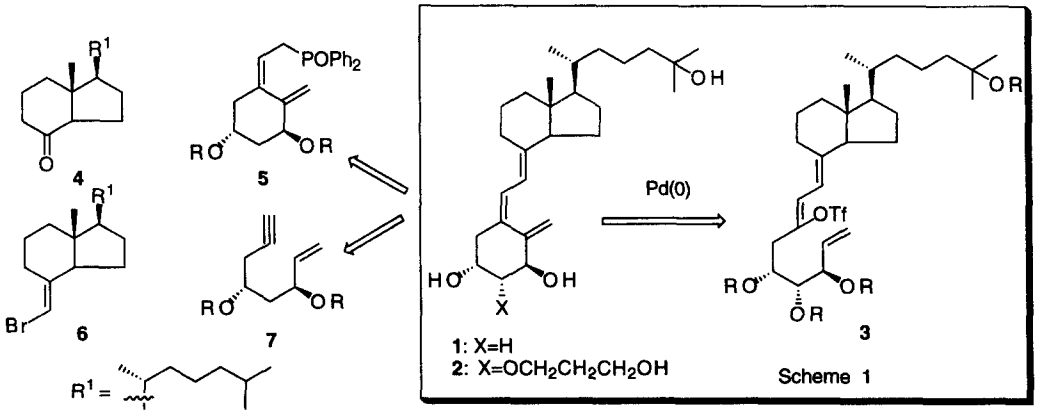
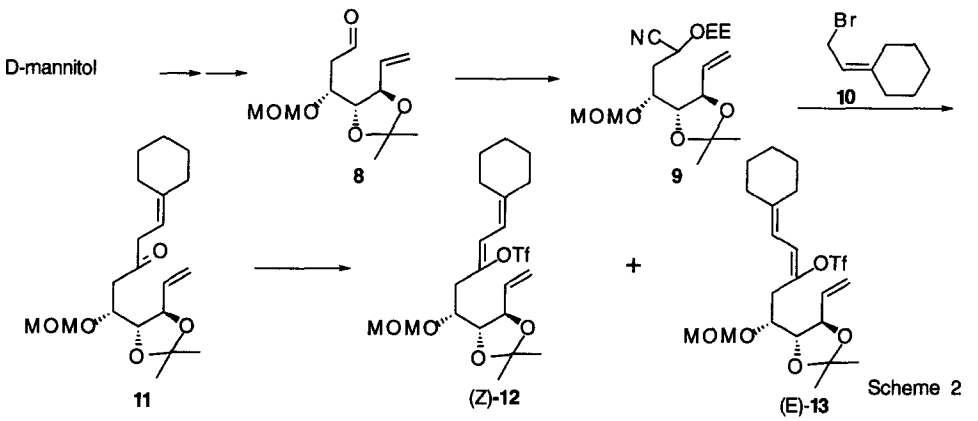
Abstract: The seco-B-ring triene system of 1α,2β,25-trihydroxy-vitamin D_3 is efficiently constructed by means of a palladium-catalyzed cyclization of the dienol triflate.

The increasing number of important potential clinical applications[1] of 1α, 25-dihydroxyvitamin D_3(Calcitriol) (**1**) and its analogues has stimulated significant effort toward the syntheses[2] of various calcitriol analogues having modified side chains and A-rings. Recent *in vivo* studies[3] on regulatory activities for calcium metabolism of 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3 (ED-71) (**2**) suggest it may be a promising drug for osteoporosis therapy.[3] One of the most crucial problem in the synthesis of vitamin D_3 is the stereoselective introduction of the seco-B-ring triene system. Construction of the triene system requires a short reaction time at a lower reaction temperature, higher temperature easily induces the "vitamin-previtamin equilibrium" *via* [1,7]-sigmatropic hydrogen shifts. Among the reported synthetic approaches to the triene system,[4] the phosphine oxide approach[4a] using **4** and **5** and the Pd-catalyzed cyclization approach[4d] using **6** and **7** are the most useful and versatile. In our synthetic plan for **2**[5] (Scheme 1), the triene system is constructed by Pd-catalyzed cyclization of the (Z)-dienol triflate **3**. In this communication, we describe the results of our initial efforts towards a total synthesis of **2**; the stereoselective synthesis of the model triene **18b** by using Pd-catalyzed cyclization of the (Z)-dienol triflate **12** (Scheme 3).



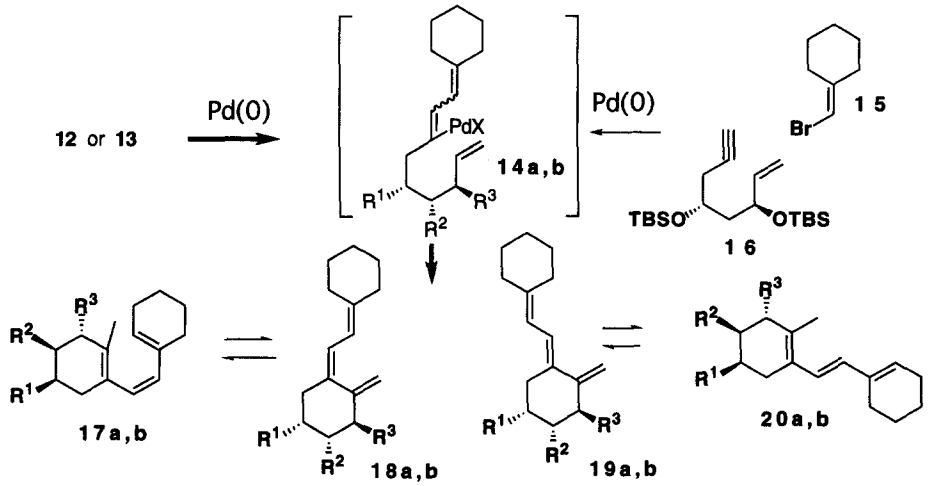
Scheme 1

To establish the feasibility of our cyclization, the (*Z*)- and (*E*)-dienol triflate **12** and **13** were prepared in the following manner (Scheme 2). The aldehyde **8** was prepared from readily available 1,2;3,4;5,6-tri-*O*-isopropylidene-D-mannitol by our previous procedure.[6] Cyanohydrin formation from aldehyde **8** (NaCN, $NaHSO_3$) and protection of the resulting alcohol (ethyl vinyl ether / H^+) gave the protected cyanohydrin **9** in 80% overall yield. The alkylation[7] of **9** with bromide **10** using potassium hexamethyldisilazide ($KN(TMS)_2$ / THF; 80% yield) and subsequent acid treatment of the alkylated product (*P*-TsOH / MeOH) followed by base treatment (2% NaOH / THF / H_2O) gave ketone **11** in 80% overall yield for the two steps. Regioselective enolate formation of **11** with $KN(TMS)_2$ at -78 °C in THF and quenching with *N*-phenyltrifluromethanesulfonimide gave a 5:1 mixture of the (*Z*)- and (*E*)-dienol triflate **12** and **13** in 67% combined yield.[8]



Scheme 2

Pd-catalyzed cyclization was performed as follows (Scheme 3). To a stirred solution of 10 mol% $Pd(OAc)_2$ and 20 mol% triphenylphosphine in DMF-triethylamine was added a solution of the (*Z*)-dienol triflate **12** in DMF. After stirring for 1 h at 20 °C, standard workup gave the (*Z*)-triene **18b** in 95% yield. The reaction

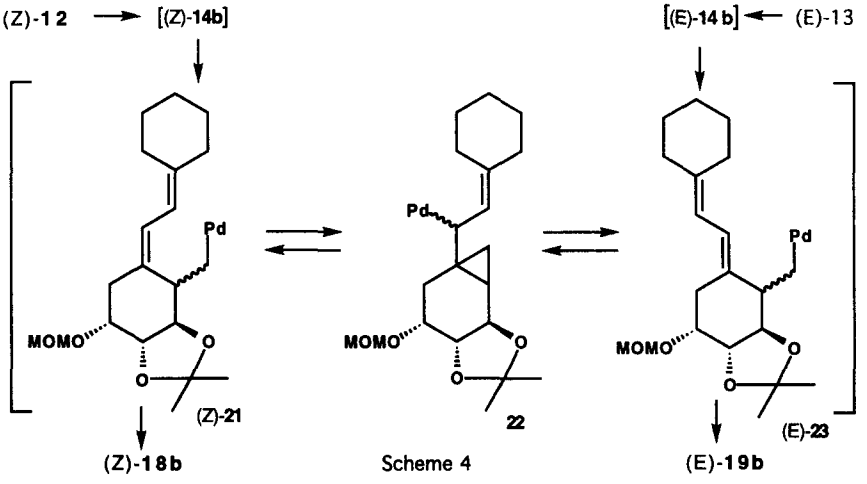


a : R^1= R^3= OTBS, R^2= H, b : R^1= OMOM, R^2= R^3= $OCMe_2O$

Scheme 3

at 50 °C gave a 93:7 mixture of (*Z*)-**18b** and (*E*)-**19b**. At a higher temperature (110 °C), a 70:20:10 mixture of (*Z*)-**18b**, (*E*)-**19b** and **17b** was formed in 99% combined yield. Similarly, performing the reaction with the (*E*)-dienol triflate **13** at 20° C gave the (*E*)-triene **19b** exclusively. At 110 °C, however, a mixture of (*E*)-**19b** and (*Z*)-**18b** was formed in a ratio of 90:10. The (*Z*)- and (*E*)-stereochemistry of the major trienes **18b** and **19b** was confirmed[9] by comparison of its ^{1}H-NMR spectrum with that of the trienes **18a** and **19a** reported by Trost's group.[4d] Thus the Pd-catalyzed cyclization using the dienol triflate proceeds with high stereoselectivity (>95%) at 20 °C and the [1,7]-sigmatropic hydrogen shift products, **17b** and **20b**, were not formed. The Pd-catalyzed alkylative enyne cyclization reported by Trost[4d] using **15** and **16**, required higher temperature (90-110 °C), and a provided 18: 50 mixture of the two major products **18b** and **17b** with trace amounts of two additional isomers **19b** and **20b**.

Based on Negishi's mechanism,[10] our speculation for the formation of the (*E*)-triene **19b** at 110 °C from the (*Z*)-dienol triflate **12** with inversion of the alkene configuration is as follows (Scheme 4). Cyclic carbopalladation ((*Z*)-**12** → (*Z*)-**14b** → (*Z*)-**21**), involving the addition of **12** to the Pd(0) species followed by addition of the resulting (*Z*)-alkenylpalladium **14b** to the terminal alkene with overall retention of the (*Z*)-dienyl configuration, gave the alkylpalladium intermediate (*Z*)-**21**. At this stage, two competitive processes are feasible; one is β-elimination of the palladium species giving the (*Z*)-triene **18b** and the other is cyclopropanation of alkylpalladium (*Z*)-**21** affording the cyclopropylcarbinyl palladium **22**. The reversible "cyclopropylcarbinyl to homoallyl palladium" rearrangement of **22** to the alkylpalladium intermediates (*Z*)-**21** and (*E*)-**23**, followed by β-elimination of the palladium species gave the trienes (*Z*)-**18b** and (*E*)-**19b**, respectively. At 20 °C, however, the β-elimination process is faster than the cyclopropanation. Consequently, the reaction of (*Z*)-**12** at 20°C gave exclusively the (*Z*)-triene **18b**, although the reaction carried out at 110 °C afforded a mixture of (*Z*)-**18b** and (*E*)-**19b**. Similarly, the formation of the (*Z*)-triene **18b** from the (*E*)-dienol triflate **13** at 110 °C and the exclusive formation of (*E*)-**19b** from (*E*)-**13** at 20 °C can be rationalized.



Scheme 4

Thus the palladium-catalyzed cyclization using the dienol triflate is useful to construct the thermally labile triene system of vitamin D3. We also found that the homoallyl palladium intermediates, like **21** and **23**,

undergo the cyclopropanation at higher temperature (>80 °C), while at lower temperature (<50 °C) the β-elimination of the homoallyl palladium species becomes dominant. Further studies on the total synthesis of ED-71 using Pd-catalyzed cyclization of dienol triflates are underway in our laboratory.

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8) **12b** ^{1}H-NMR($CDCl_3$, 270 MHz) δ=6.24 (1H, d, J = 11.2 Hz), 5.96 (1H, d, J = 11.2 Hz), 5.79-5.92 (1H, m), 5.43 (1H, d, J = 17.2 Hz), 5.30 (1H, d, J = 10.2 Hz), 4.75 (1H, d, J = 6.9 Hz), 4.61 (1H, d, J = 6.9 Hz), 4.35 (1H, t, J = 7.6 Hz), 3.98-4.03 (1H, m), 3.83-3.87 (1H, m), 3.33 (3H, brs), 2.50-2.80 (2H, m), 2.10-2.40 (4H, m), 1.40-1.80 (12H, m). IR (neat) 3026, 2890, 1629, 1564 cm^{-1}.
13b ^{1}H-NMR($CDCl_3$, 270 MHz) δ=6.47 (1H, d, J = 11.6 Hz), 5.70-6.00 (2H, m), 5.43 (1H, d, J = 16.2 Hz), 5.29 (1H, d, J = 10.2 Hz), 4.60-4.80 (2H, m), 4.30-4.40 (1H, m), 3.90-4.10 (1H, m), 3.80-3.90 (1H, m), 3.35 (3H, brs), 2.90 (1H, dd, J = 7.9 Hz), 2.63 (1H, dd, J = 3.96, 15.8 Hz), 2.00-2.40 (4H, m), 1.30-1.70 (12H, m). IR (neat) 3024, 2854, 1620, 1552 cm^{-1}.

9) **18b** ^{1}H-NMR($CDCl_3$, 270 MHz) δ=6.32 (1H, d, J = 11.0 Hz), 6.20 (1H, d, J = 11.0 Hz), 5.31 (1H, t, J = 1.9 Hz), 4.98 (1H, t, J = 1.9 Hz), 4.82 (1H, d, J = 6.7 Hz), 4.70 (1H, d, J = 6.7 Hz), 4.40 (1H, dt, J = 9.9, 1.9 Hz), 4.30-4.33 (1H, m), 3.58 (1H, dd, J = 2.3, 10 Hz), 3.39 (3H, br s), 2.50-2.60 (2H, m), 2.10-2.40 (4H, m), 1.40-1.70 (12H, m). IR (neat) 3032, 2888, 1643 cm^{-1}.
19b ^{1}H-NMR($CDCl_3$, 270 MHz) δ=6.62 (1H, dd, J = 11.7, 2.5 Hz), 5.96 (1H, d, J = 11.7 Hz), 5.07 (1H, t, J = 1.7 Hz), 4.94 (1H, t, J = 1.7 Hz), 4.85 (1H, d, J = 6.9 Hz), 4.72 (1H, d, J = 6.9 Hz),4.51-4.56 (1H, m), 4.35-4.39 (1H, m), 3.55-3.60 (1H, m), 3.38 (3H, br s), 3.08-3.16 (1H, m), 2.10-2.40 (5H, m), 1.40-1.80 (12H, m). IR (neat) 3024, 2854, 1630 cm^{-1}.

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