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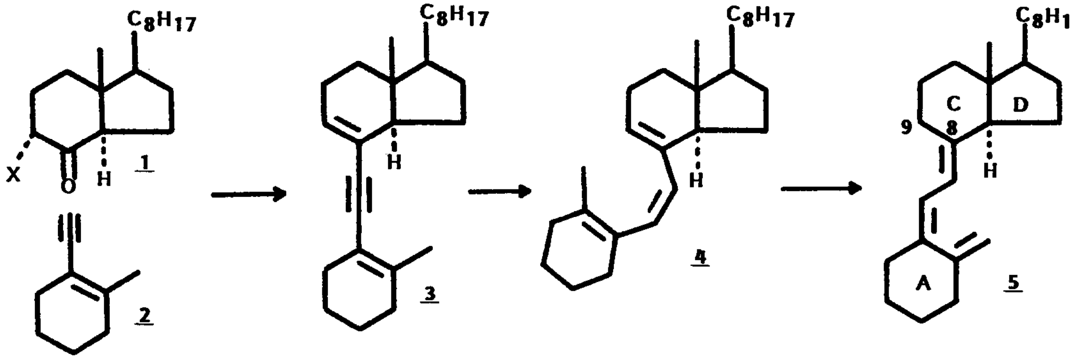
PALLADIUM-CATALYZED SYNTHESIS OF DIENYNES RELATED TO VITAMIN D FROM ENOL TRIFLATES

L. Castedo, A. Mouriño, and L.A. Sarandeses

Departamento de Química Orgánica. Facultad de Química y
C.S.I.C. (Sección de Alcaloides). Santiago de Compostela. Spain.

Summary: This note describes a simple synthesis of Lythgoe-type dienynes based on palladium catalyzed coupling of kinetic Grundmann's ketone enol triflate and acetylenic compounds containing the vitamin D A-ring fragment.

It is known that the Lythgoe type enynes 3 are useful key intermediates in the total synthesis of vitamin D metabolites.[1,2] These enynes can easily be transformed into the desired vitamin D compounds 5 by successive semi-hydrogenation and thermolysis.[2] The difficulties of this approach[2] are (i) the many steps needed for the preparation of the enyne precursor choroketone 1 (X=Cl) (7%), and (ii) the moderate yield of dienyne 3 (20%) obtained by successive coupling between an acetylenic frangment such as 2 and chloroketone 1 (X=Cl) followed by formal elimination of ClOH.



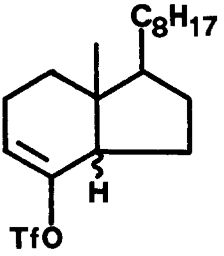
Impressive results have recently been reported by Stille and co-workers for the reaction of enol triflates with acetylenic stannyl derivatives[3] or simple acetylenes[4]. On the basis of these results we surmised that the kinetic enol triflate of Grundmann's ketone (1, X=H)[5] would react with suitable derivatives of conjugated acetylenes of type 2 to afford the desired enynes 3. We report here the results of our investigations, which have led to the rapid synthesis of enynes of type 3 in excellent yield.

Enolate formation of Grundmann's ketone (1, X=H) under kinetic conditions (LDA, 1.1 equiv, THF, -80 ºC: 15 min, RT: 1 h 45 min) followed by the slow addition of N-phenyltrifluoromethanesulfonimide[6] ($PhNTf_2$, 1.06 equiv) in THF at -80 ºC and stirring for 12 h at 0 ºC afforded 6a[7] in 88% yield. The silyl organotin compound 7b was prepared in 98% yield by metallation of the known silyl ether 7a[8a] with n-butyllithium (1 equiv, THF, -80 ºC, RT: 1 h) and subsequent reaction of the resulting lithium derivative with tri-n-butyltin chloride (1.05 equiv, -80 ºC, RT: 24 h). Coupling[3] between triflate 6a and the stannyl derivative 7b (1.1 equiv) in the presence of dry lithium chloride (7 equiv) and $Pd(PPh_3)_4$ (1.6% equiv) in refluxing THF for 20 h afforded, after deprotection ($n\text{-}Bu_4NF$) and flash chromatography (hexanes-12% EtOAc/hexanes), the desired epimeric mixture of dienyne alcohols 9a[7] in 77% yield. Compound 11[7] was also obtained under similar conditions in 74% yield in 9 h by successive treatment of triflate 6a with $n\text{-}Bu_3C{\equiv}CSiMe_3$[9] (3 equiv) and deprotection ($n\text{-}Bu_4NF$).

Even more gratifying was the result obtained by direct coupling between triflate 6a and 8 which was the precursor used for the preparation of 7b. Thus, reaction of triflate 6a with the unsaturated acetylenic ketone 8[8] (1 equiv) under the catalytic influence of $Pd(PPh_3)_2Cl_2$ (2% equiv) in the presence of triethylamine (3.4 equiv) in DMF at 75 ºC[4] for 4 h gave, after flash chromatography (5% EtOAc/hexanes), the dienynone 10a[7] in 80% yield. In view of the presence of the carbonyl group in 8, the success of this reaction is an indication of the mildness of this catalyzed coupling process. Compound 10a might also be synthesized by coupling the enyne 11 with 12[10] by previously used procedures.[8a,b]

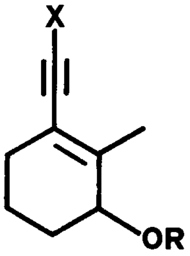
Further support for structures 9a and 10a was achieved by transformation of 9a into 10a (PDC-PPTS/CH_2Cl_2) and 10a into 9a ($NaBH_4$-Ce^{3+}/MeOH). The lack of epimerization of the CD-trans-fusion during the above reaction conditions was confirmed by synthesis of the epi-derivatives 9b and 10b: triflate 6b[7] obtained from epi-Grundmann's ketone[10] (LDA, $PhNTf_2$) was subjected to the transformations described above for the synthesis of 10a to afford 10b[8a] in 91% yield, and this compound was easily converted to 9b[7] by reaction with $NaBH_4$-Ce^{3+}/MeOH. The synthesized epi-derivatives 9b and 10b are clearly distinguished from the CD-trans-fused analogues 9a and 10a by ^1H-NMR.[7]

In conclusion, the described sequence achieves the regiospecific introduction of the C_8-C_9 double bond under mild conditiond and could be used to synthesize the principal metabolites of vitamin D and various analogues modified at the A-C rings. Further research on the application of this methodology to the synthesis of 1,25-dihydroxyvitamin D (the hormonally active form of vitamin D) and of several analogues modified at the C-ring is under way.[11]



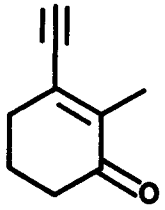
6a, H (α)

6b, H (β)



7a, R= $SiMe_2t\text{-}Bu$, X= H

7b, R= $SiMe_2t\text{-}Bu$, X= $SnBu_3$



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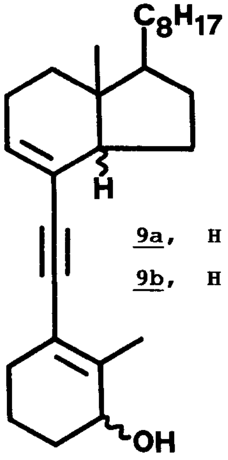
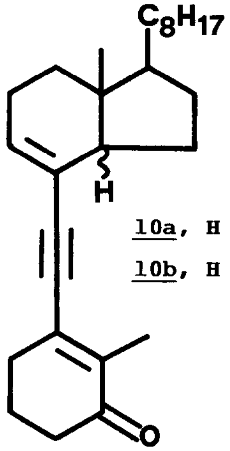


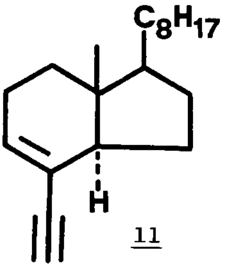
9a, H (α)

9b, H (β)



10a, H (α)

10b, H (β)



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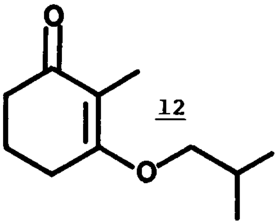

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5. This ketone and other closely related compounds are readily obtained by degradation of vitamin D_3 and vitamin D_2 and constitute important intermediates for the synthesis of compounds with vitamin D activity.[1]

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7. 250 MHz ^{1}H-NMR ($CDCl_3$, δ): 6a: 5.58 (1H, m, vinyl H), 0.76 (3H, s, $C_{18}CH_3$); 6b: 5.71 (1H, m, vinyl H), 0.98 (3H, s, $C_{18}CH_3$); 11: 6.07 (1H, m, vinyl H), 0.69 (3H, s, $C_{18}CH_3$); 9a: 5.97 (1H, m, vinyl H), 1.99 (3H, m, $C_{19}CH_3$), 0.70 (3H, s, $C_{18}CH_3$); 9b: 6.06 (1H, m, vinyl H), 1.99 (3H, m, $C_{19}CH_3$), 0.92 (3H, s, $C_{18}CH_3$); 10a: 6.14 (1H, m, vinyl H), 1.95 (3H, m, $C_{19}CH_3$), 0.70 (3H, s, $C_{18}CH_3$); 10b: 6.22 (1H, m, vinyl H), 1.96 (3H, m, $C_{19}CH_3$), 0.94 (3H, s, $C_{18}CH_3$). All new compounds had satisfactory mass spectra.

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9. This reagent was prepared in 62% yield by reaction of Me_3SiC_2Li with $ClSnBu_3$ in THF.

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11. We are grateful to the Comisión Asesora de Investigación (CAICYT) for financial support. We thank Hoffmann La Roche (Basel) for the generous gift of vitamin D_3 and Dr. W.H. Okamura for helpful suggestions. We also acknowledge the initial work of R.J. Garcia Cota in this area.

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