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A General Synthetic Route to A-Ring Hydroxylated Vitamin D Analogs from Pentoses

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Abstract: The enyne needed for coupling to a CD-ring fragment, namely, 3S, SR-oct-1-en-7-yne-3,5diol, in the Trost-Dumas carbopalladation route to 1α , 25-dihydroxyvitamin D₃ was synthesized from D-xylose in 13 steps and 21% yield.

 1α , 25-Dihydroxyvitamin D3 (3a), the hormonally active metabolite of vitamin D3, is classically associated with calcium homeostasis.^{1a,b} Recently its effect upon cellular differentiation has been established^{2a,b}, and this fact has elicited renewed interest in the synthesis of members of this class of compounds. The goal is the discovery of an efficient and scalable process which is sufficiently flexible to allow access to a range of analogs and potential metabolites. This synthetic effort is particularly important because of the narrow therapeutic range between efficacy and toxicity.³ The evolution of synthetic approaches to 1α -hydroxyvitamin D analogs has resulted in a number of convergent modular syntheses in which an A-ring synthon is joined to the CD-ring system which in turn possesses an appropriately substituted C17 side chain.⁴ This methodology conceptually derives from Lythgoe's classical synthesis of vitamin D.⁵ Among the many A-ring synthon routes a brilliant culmination of this approach was achieved by Trost, et al.⁶ in their cyclization of a carbopalladated enyne to yield 3a and 3c (Scheme 1).



Scheme 1

In effect, the methodological problem can be considered solved, however, accession of the stereodifferentiated 1, 3-anti-diol system of the 1, 7-enyne remains a critical synthetic task.

We report a singularly facile route to 3S, SR-oct-1-en-7-yne-3, 5-diol (2a) from D-xylose. Furthermore 1 β , 3 α -epi-vitamin D's can potentially be made from L-xylose.⁷ The synthetic scheme is expressed in the

mapping of the stereogenic centers of 3-deoxy-D-xylono- γ -lactone (7) to those of the enyne steroidal A-ring synthon (using the steroid numbering system) (Scheme 2).



Starting with a D-pentose and conversion to the D-pentono- γ -lactone using the chemistry in Scheme 3 results in the *R* configuration at the C3 position of the enyne which corresponds to the natural C3-hydroxyl group configuration in the vitamin D series. Starting with an L-pentose and conversion to the L-pentono- γ -lactone yields the opposite C3 stereochemistry corresponding to the epi-vitamin D series. The point of attachment of the acetylene unit is at the site of the primary alcohol and a methylene group ultimately replaces the carbonyl group.

Synthesis of the enyne-1, 3-diol needed for 1α -hydroxy vitamins 3a and 3c proceeded from D-xylose (4) which was converted via bromine oxidation to 3R, 4S, 5R-3, 4-diacetoxy-5-acetoxymethyl-2-tetra-hydrofuranone (5). Subsequent steps are summarized in Scheme 3.



Scheme 3

Catalytic reduction of 5 in the presence of triethylamine yields 3*R*, 5*R*-3-acetoxy-5-acetoxymethyl-2tetrahydrofuranone (6) in a process which serves to invert the configuration at C3 to yield the desired β epimer and eliminate the unneeded hydroxyl group (in the case of the synthesis of 1 α -hydroxyvitamin D, 3c). DIBAL reduction, deprotection of the C6 hydroxyl group, mesitylenesulphonyloxylation, intramolecular oxide formation, and regioselective addition of acetylide anion yielded 2b. Coupling of 2b with 7-(*E*)-bromodes-AB-cholest-7-ene (1a) according to the Trost procedure⁶ yielded 1 α -di[(2-methoxyethoxy)methoxy]vitamin D3 (3d) (51%). Deprotection with ZnBr2 in CH₂Cl₂ yielded 1 α -hydroxyvitamin D3 (3c) (91%).

Transformation 5 yields 6 deserves comment. The role of the triethylamine is to effect a β -elimination to yield the enol acetate, which then undergoes catlytic hydrogenation from the less hindered face of the five membered ring, thus establishing the β -configuration of the acetoxy group as shown in Scheme 4.



No epimerization at C5 occurs, in fact, it has been shown by Bock, et. al. that the four possible triacetoxy-D-pentono- γ -lactones related to 5 yield the same product, namely, 3R, 5R-3-acetoxy-5-acetoxymethyl-2-tetrahydrofuranone 6.¹¹

In conclusion, we report a synthetic approach to A-ring metabolites which potentially extends the Trost method to all the 1α -hydroxyvitamin D's and 1β -hydroxyepivitamin D's. The adaptation of the natural stereochemistry of a polyol chiron to vitamin D synthesis has been used elegantly by De Luca's group in the case of (-) quinic acid for the synthesis of 1α , 25-dihydroxy-19-nor-vitamin D₃.¹² Likewise, Desmale and Tanier have used (-) methyl shikimate as an A-ring synthon in a Lythgoe type synthetic approach to 1α -hydroxyvitamin D₃.¹³ Perhaps closest to the present work is the palladium catalysed cyclization of an enevinyl iodide derived from D-mannitol to yield an A-ring synthon for 1α , 2β , 25-trihydroxyvitamin D₃.¹⁴

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- 3. For osteoporosis, the therapeutic dose of **3a** is between 0.5 µg and 0.75 µg/day. Toxicity appears in the form of hypercalcemia around 0.75 µg/day (Aloia, J. F., *Metabolism*, **1990**, *39*, 35).
- 4. For a list of recent syntheses of A-ring synthons see ref. 6.
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- In addition to 1α, 25-dihydroxy vitamin D3, the other three diastereometric diols, namely, 1β, 3β; 1α, 3α; 1β, 3α have been synthesized: Muralidharan, K. R.; deLera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W. H., J. Org. Chem. 1993, 58, 1895.
- 11: [α]_D²⁴=-131° (c=1.7, CHCl3); IR: (neat) 3433 cm⁻¹ (OH); ¹H NMR (CDCl3): δ, 1.44 and 1.63 (ddd, 2H, J1=3.2 Hz, J2=9.7 Hz, J3=14 Hz, 4-H2), 3.3 (s, 3H, OCH3 (MEM)), 3.37-3.78 (m, 9H, CH2CH2 (MEM), 5-H, 6-H2, 5-OH, and 6-OH), 4.33 (m, 1H, 3-H), 4.60 and 4.66 (d, 2H, J=6.7 Hz, OCH2 (MEM)), 5.15 (m, 2H, 1-H2), 5.73 (ddd, 1H, J1=7.2 Hz, J2=10.2 Hz, J3=17.3 Hz, 2-H); ¹³C NMR: 139.7, 116.3, 93.0, 74.1, 72.2, 68.6, 67.37, 67.32, 58.7, 40.1; MS (CI): 221 (M⁺+1, 100%); MS (FAB): 221 (M⁺+1, 100%); HRMS: calculated, 221.1388; observed, 221.1383.
- 9. 13: $[\alpha]_D^{24}=-127.2^{\circ}$ (c=1.07, CHCl3); IR: (neat) 2926, 2885, 1107, 1032 cm⁻¹; ¹H NMR (CDCl3): δ , 1.65 and 1.85 (m, 2H, 4-H₂), 2.42 and 2.71 (dd, 2H, J₁=2.6 Hz, J₂=5.0 Hz, J₁'=4.6 Hz, J₂'=4.8 Hz, 6-H₂), 2.9 (m, 1H, 5-H), 3.29 (s, 3H, OCH₃ (MEM)), 3.45-3.75 (m, 4H, CH₂CH₂ (MEM)), 4.22 (m, 1H, 3-H), 4.60 and 4.71 (d, 2H, J=6.9 Hz, OCH₂ (MEM)), 5.15 (dd, 2H, J₁=17.0 Hz, J₂=25.4 Hz, 1-H₂), 5.64 (ddd, 1H, J₁=7.5 Hz, J₂=10.1 Hz, J₃=17.3 Hz, 2-H); ¹³C NMR: 137.4, 117.2, 92.5, 74.4 71.5, 66.7, 58.7, 49.0, 47.1, 38.6; Analysis: calculated, C 59.39, H 8.97; observed, C 59.45, H 9.07.
- 2b: [α]_D²⁴=-60° (c=0.57, CHCl₃); IR: (neat) 3265, 2926, 2887, 2820, 1199, 1107, 1039, 929 cm⁻¹; ¹H NMR (CDCl₃): δ, 1.74 (m, 2H, 4-H₂), 1.93 (t, 1H, J=2.6 Hz, 8-H), 2.44 (ddd, 1H, J₁=2.6 Hz, J₂=6.1 Hz, J₃=16.8 Hz, 6-H₂), 3.27 (s, 3H, OCH₃ (MEM)), 3.28 (s, 3H, OCH₃ (MEM)), 3.41-3.80 (m, 9H, CH₂CH₂ (MEM) and 5-H), 4.1 (m, 1H, 3-H), 4.56 and 4.66 (d, 2H, J=6.8 Hz, OCH₂ (MEM)), 5.1 (m, 2H, 1-H₂), 5.6 (ddd, 1H, J₁=7.6 Hz, J₂=10.0 Hz, J₃=17.4 Hz, 2-H); ¹³C NMR: 137.9, 116.8, 95.4, 92.8, 80.3, 74.2, 73.2, 71.4, 70.09, 70.05, 66.99, 66.93, 58.6, 40.3, 25.1; MS (FAB): 315 (M⁺-1, 100%); Analysis: calculated, C 60.74, H 8.92; observed, C 60.70, H 8.85.
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