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# Toward a General Synthesis of A-Ring Trihydroxylated Vitamin D Analogs: Synthesis of an A-Ring Synthon of ED-71 from D-Arabinose

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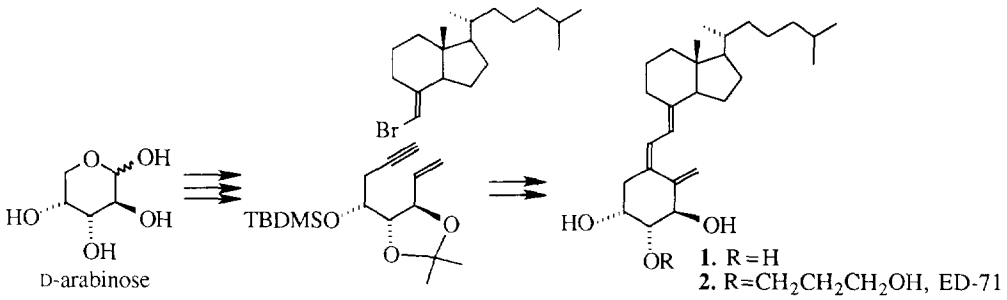
**Abstract:** (3*R*, 4*S*, 5*R*)-3, 4-(*O*-isopropylidene)-5-(*tert*-butyldimethylsiloxy)-1-octene-7-yne was synthesized from D-arabinose in 9 steps and 28% yield and coupled *via* the Trost-Dumas carbopalladation method to a steroidal CD-ring fragment to yield 1α, 2β-dihydroxyvitamin $D_3$.

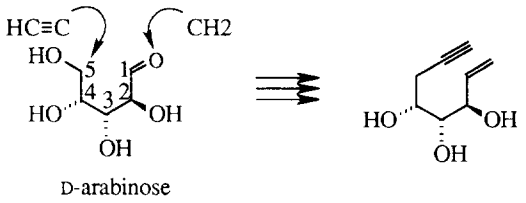
The role of 1α, 25–dihydroxyvitamin $D_3$ (1, 25-$D_3$) in calcium metabolism, bone remodeling, and homeostasis of minerals in the kidney is well established.[1a,b] Recent interest[2] in the vitamin D series has gone beyond calcium metabolism because of the discovery of intracellular vitamin D receptors in a wide range of tissues and cultured cells including human breast cancer cells.[3] Accordingly, members of this class of compounds may be effective in the treatment of psoriasis[4] and certain cancers[5], or as immunomodulators.[6a,b] The problem with 1, 25-$D_3$ as a therapeutic agent for cell proliferation and differentiation is that hundred-fold higher amounts are required relative to those needed in calcium mobilization. These higher doses would result in potentially fatal hypercalcemia. The search for non-calcemic and potent inducers of monocytic differentiation is driven by this circumstance.[7] Several convergent syntheses have been developed which allow attachment of an A-ring synthon to a CD-ring part bearing a suitable side chain.[8] All of the A-ring diastereomers of 1α, 25–dihydroxyvitamin $D_3$ have been synthesized[9] and much recent attention has been paid to trifunctionalized A-ring analogs.[10a-e] There exists, however, no general method for producing a library of stereodifferentiated, trifunctionalized A-ring synthons. We have previously shown that the stereocenters of an aldopentose can be mapped to a 1,7-enyne-diol[11] suitable for coupling to a CD fragment via the Trost-Dumas carbopalladation method[12] to yield 1α, 25-dihydroxyvitamin $D_3$. In an extension of that work, we present herein a concise, efficient route to a trihydroxylated A-ring synthon from D-arabinose (Scheme 1). The vitamin D analog thus produced, 1α, 2β-dihydroxyvitamin $D_3$ (**1**) is of interest in that it possesses the same stereochemical array of hydroxyl groups in the A-ring as the osteoporotic drug ED-71 (**2**).[10a]




**Scheme 1**

The aldopentoses serve as appropriate starting materials for trihydroxylated 1,7-enynes in that they

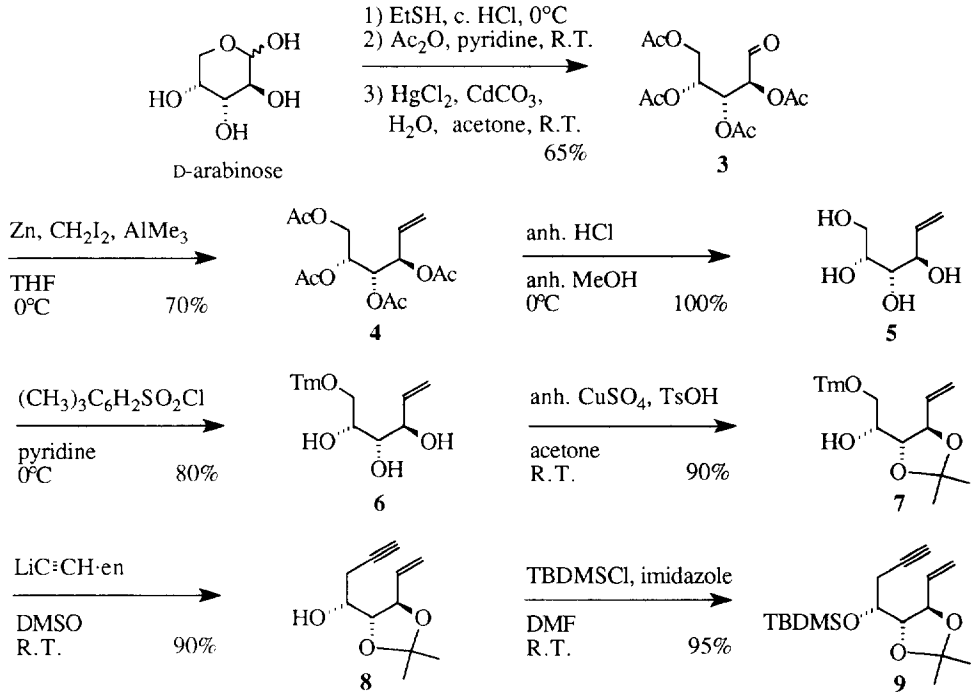
contain the desired number of chiral centers and all eight diastereomers are readily available. The mapping of the stereocenters of D-arabinose to those of the A-ring synthon can be summarized as follows (Scheme 2).




D-arabinose

**Scheme 2**

Effectively, one need only to methylenate the $C_1$ aldehyde and attach the acetylenic unit at $C_5$ *via* replacement of the hydroxyl group. D-Arabinose was converted to *aldehydo*-D-arabinose tetraacetate by the known procedure[13a,b] and subsequent steps are shown in Scheme 3.



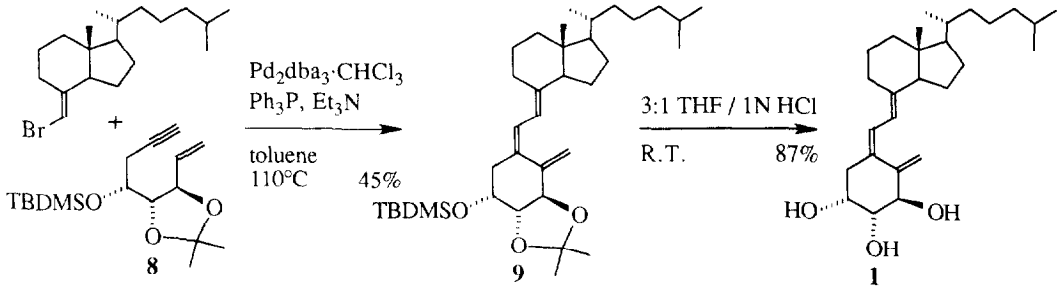

**Scheme 3**

Zinc based methylenation[14] of **3** gave **4**[15] in good yield. It should be noted that in this transformation the strongly basic conditions of the Wittig reaction with a non-stabilized ylide are avoided thus reducing the possibility of epimerization of the α center or β-elimination of the acetate group. β-Elimination is well documented for this system and has been used effectively by us,[11] and occurs readily even on permethylated *aldehydo* sugars.[16] The methylenation reaction is also amenable to scale-up and was run on scales as large as 37mmol with no decrease in yields, although care must be exercised when generating the active metal-methylene species due to the highly exothermic reaction. It was noted, however, that over the course of the

reaction, partial cleavage of the acetate groups occurred. Therefore, we found it most practical to treat the crude product with pyridine-acetic anhydride prior to purification by recrystalization.

Deprotection of **4** by acid catalyzed transesterification, followed by selective sulfonate ester formation at the primary hydroxyl yielded **6**. Acetonide **7** was formed selectively on the *trans* 1,2-diol as confirmed by homonuclear decoupling experiments with the exchangeable proton. Addition of **7** to an excess of lithium acetylide ethylene diamine complex in DMSO gave **8**. Finally, protection of the alcohol as the silyl ether completed the synthesis of enyne (**9**).[17]

Coupling of **9** with the vinyl bromide obtained from Grundmann's ketone under the conditions of Trost, et al.[12] gave the protected vitamin in 45% yield. Deprotection proceeded in one step under acidic conditions to give **1**, whose spectroscopic data[18] were in accordance with those reported previously[19] (Scheme 4).




**Scheme 4**

In summary, the present work extends the palladium catalyzed cyclization of 1,7-enynes to stereodifferentiated vitamin D analogs bearing three hydroxyl groups on the A-ring. The adaptation of a polyol chiron has been elegantly used by other workers to produce A-ring synthons.[10b,d,e; 20a-c] A related synthesis of an A-ring synthon for **1** proceeds from D-mannitol[10d] in steps similar to those in the present synthesis (**10** -> **13**).


The adaptation of aldopentoses as chirons for polyhydroxylated vitamin D synthesis appears quite useful. Illustrative of this fact is that **1** is prepared in a 16 step process from cholesterol including a photoisomerization of 1α, 2β, 3β-trihydroxy-cholest-5, 7-diene.[19]

## ACKNOWLEDGMENT

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15. **4**: m.p. 80.5-82.0; $[\alpha]^{25}_D$=+52.3° ($CHCl_3$, 0.0110g/ml); IR $cm^{-1}$(KBr) 1742, 1648; $^1H$ NMR δ(400MHz, $CDCl_3$) 5.69 (ddd, $J_1$=16.8, $J_2$=10.8, $J_3$=5.2, 1H, H-2), 5.50 (m, 1H, H-3), 5.33 (dd, $J_1$=8.4, $J_2$=3.2, 1H, H-4), 5.28 (d, $J$=17.2, 1H, H-1*trans*), 5.23 (d, $J$=10.8, 1H, H-1*cis*), 5.18 (ddd, $J_1$=8.4, $J_2$=5.2, $J_3$=2.8, 1H, H-5), 4.22 (dd $J_1$=12.6, $J_2$=2.8, 1H, H-6a), 4.13 (dd, $J_1$=12.6, $J_2$=5.2, 1H, H-6b), 2.07 s, 2.06 s, 2.04 s, 2.03 s (12H, C<u>H</u>3$CO_2$-); Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.15; H, 6.39. Found: C, 52.93; H, 6.3.
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17. **9**: oil, $[\alpha]^{25}_D$=-12.1° ($CHCl_3$, 0.0223g/ml); IR $cm^{-1}$(NaCl film) 3313, 2213, 1645; $^1H$ NMR δ(400MHz, $CDCl_3$) 5.92 (ddd, $J_1$=17.2, $J_2$=10.4, $J_3$=7.0, 1H, H-2), 5.41 (d, $J$=17.2, 1H, H-1*trans*), 5.24 (d, $J$=10.4, 1H, H-1*cis*),4.45 (dd, $J_1$=$J_2$=7.0, 1H, H-3), 3.99 (m, 2H, H-4 and H-5), 2.40 (m, 2H, H-6), 2.00 (dd, $J_1$=$J_2$=2.6), 0.90 (s, 9H, C(C<u>H</u>3) TBDMS), 0.11 (s, 3H, SiC<u>H</u>3 TBS) 0.10 (s, 3H, SiC<u>H</u>3 TBDMS);$^{13}C$ δ(100MHz, $CDCl_3$) 136.8, 118.0, 108.9, 81.8, 80.5, 78.2, 70.6, 70.5, 27.1, 27.0, 25.8, 24.4, 18.1, -4.4, -4.6, Anal. Calcd. for $C_{17}H_{30}O_3Si$: C, 65.74; H, 9.76. Found: C, 65.53; H, 9.90.
18. **1**: oil, $[\alpha]^{25}_D$=-91.2° ($CHCl_3$, 4.75x$10^{-3}$g/ml); IR $cm^{-1}$(NaCl film) 3395, 1644; $^1H$ NMR δ(400MHz, $CDCl_3$) 6.36 (d, $J$=11.2, 1H, H-6), 6.02 (d, $J$=11.3, 1H, H-7), 5.42 (sharp m, 1H, H-19*cis*), 5.08 (sharp m, 1H, H-19*trans*), 4.22 (m, 1H, H-1), 4.15 (m, 1H, H-3), 3.50 (m, 1H, H-2), 3.04 (broad s, exchangable, 1H, -O<u>H</u>), 2.80 (dd $J_1$=12.0, $J_2$=3.8, 1H, H-9α), 2.58 (broad s, exchangable, 1H, -O<u>H</u>), 2.48 (m, 2H, H-4a.b), (broad s, exchangable, 1H, -O<u>H</u>), 0.91 (d, $J$=6.3, 3H, 21-$CH_3$), 0.87 (d, $J$=1.7, 3H, 26-$CH_3$), 0.85 (d, $J$=1.7, 3H, 27-$CH_3$), 0.54 (s, 3H, 18-$CH_3$); $^{13}C$ δ(100MHz, $CDCl_3$) 144.4, 143.5, 131.7, 125.2, 22.7, 22.5, 22.2, 18.8, 11.8; MS (EI) 417 (M+), 399, 381, 151 (lit., ref. 16: 416 (M+), 398, 380, 150); UV λmax nm(EtOH) 265 (lit., ref. 16: 263).
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