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Communications

A Facile Synthetic Route to an A-Ring Trihydroxylated Vitamin D Analog from D-Arabinose

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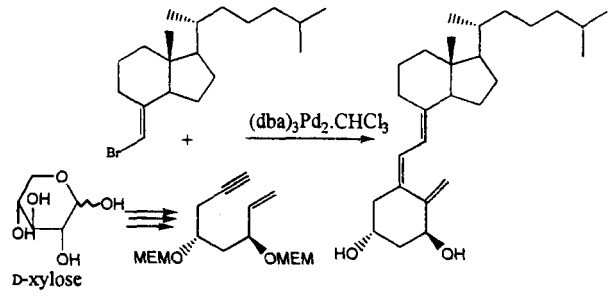
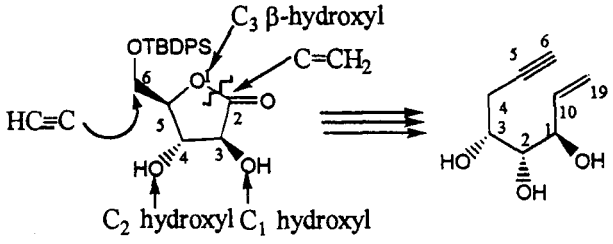
1α,25 -Dihydroxyvitamin D_3, the hormonally active metabolite of Vitamin D_3, is associated with calcium homeostasis.[2] Its effect upon cellular differentiation and proliferation has been established.[3] Furthermore, members of this class of compounds show the possible connection between Vitamin D analogs and treatment of diseases, such as psoriasis[4] or cancer[5] and also the efficacy as immunomodulators.[6] Its therapeutic use is limited by toxicity such as hypercalcimia.[7] Thus a basis exists for synthetic modification aimed at a favorable balance between efficacy and toxicity. Several convergent methods were applied to synthesize CD-ring Analogs[8] possessing an appropriately substituted C_{17} side chain and A ring analogs[9] which have different stereochemistry in C_1 and C_3 position in A ring. Among the many A ring synthon routes a brilliant coupling method was achieved by Trost, *et al.* [10] *via* palladium catalyzed cyclization and simultaneous attachment of an acyclic 1,7-enyne to a Grundman ketone derivative. We have previously shown that a singularly facile route to 1,7-enyne from D-xylose is suitable for coupling to a CD ring fragment *via* the Trost-Dumas carbopalladation method to yield 1α -hydroxyvitamin D_3 (Scheme 1).[11] Much recent attention to trifunctionalized A ring analogs[12a-e] spurs the synthesis of 1,7-enyne-triol and its coupling to CD ring fragment. Recently the synthesis of 1,7-enyne-triol starting from D-arabinose and its attachment to CD-ring part to give 1α, 2β -dihydroxyvitamin D_3 was reported by our group.[13]

In this paper, we present more efficient route to a 1α,2β, 3β -trihydroxy-1,7-enyne from D-arabinose. Furthermore the complete series of 1,2,3-epi-trihydroxy1,7-enynes can potentially be made from the appropriate D-pentose and L-pentose. The synthetic scheme is expressed in the mapping of the stereogenic centers of a generalized D-aldolactone (using the tetrahydrofuranone numbering system) to those of a generalized steroidal A-ring segment (using the steroid numbering system) (Scheme 2).

Starting with a D-pentose the stereochemistry at C_3 of the derived enyne is constant and β as in the natural vitamin D



Scheme 1.



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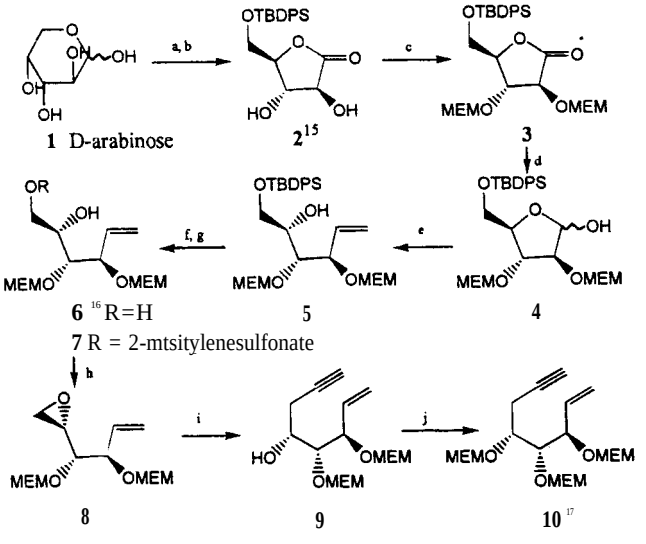
Scheme 2.

series. The stereochemistry at C_1 and C_2 of the enyne A-ring synthon in Scheme 3 is variable depending upon the choice of the starting D-pentose. The point of attachment of the acetylene unit is at C_6 of the tetrahydrofuranone and the C_2 atom of the carbonyl group is ultimately the site of methylenation.

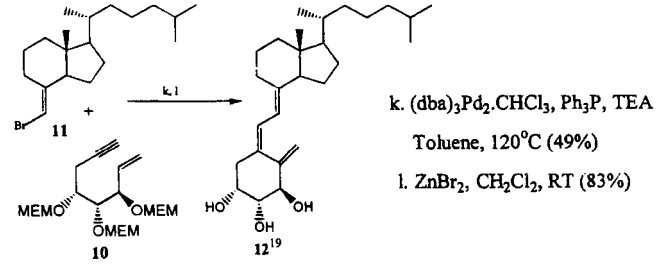
Synthesis of the 1,2,3-trihydroxy-1,7-enyne needed for 1α,2β-dihydroxyvitamin D_3 proceeded from D-arabinose **(1)** which was converted by known bromine oxidation[14] followed by selective protection of primary hydroxy group to (3S,4R,5S)-3,4-dihydroxy-5-[(*t*-butyldiphenylsiloxy)methyl]-2-tetrahydrofuranone **(2).**[15] Subsequent steps were summarized in Scheme 3.

Diol protection of **2** with MEMCl, DIBAL reduction, methylenation,[11a] and deprotection of the C_6 hydroxy group gave compound **6.**[16] Selective mesitylenesulfonylation of the C_6 hydroxy group with sterically hindered mesitylenesulfonyl chloride, intramolecular epoxide formation, regioselective addition of acetylide anion, and protection of hydroxy group completed the synthesis of 1,7-enyne **(10).**[17]

Coupling of **10** with 7-(2)-bromo-des-AB-cholest-7-ene **(11)**[10,11] according to the Trost procedure followed by deprotection with $ZnBr_2$ yielded 1α,2β-dihydroxyvitamin D_3 **(12),**



Scheme 3. [a]Br_2, K_2CO_3, H_2O, RT. [b]*t*-$BuPh_2SiCl$, imidazole, DMF, RT (a+b, 65%). [c]MEMCl, *i*-Pr_2NEt, CH_2Cl_2, Reflux (92%). [d]DIBAL, CH_2Cl_2, − 65 °C (98%). [e]Ph_3PCH_3Br, *t* BuOK THF, 0 °C (65%). [f]*n*-Bu_4NF, THF, RT (96%). [g]2-mesitylenesulfonylchloride, pyridine, − 5 °C (98%). [h]K_2CO_3, ab EtOH, RT (98%). [i]HC ≡ CLi.ethylenediamine complex, DMSO, RT (92%). [j]MEMCl, *i*-Pr_2NEt, CH_2Cl_2, Reflux (92%).



Scheme 4.

whose spectroscopic data were in accordance with those reported previously (Scheme 4).[13,18,19]

In conclusion, the presented synthesis of the A-ring synthon is indeed a facile method for production of various analogs of vitamin D, differing in the stereochemistry at 1,2, 3 positions of the A-ring. This methodology is valuable from the standpoint that many A-ring diastereomers can be connected with any number of CD fragment analogs to produce a range of compounds with perhaps interesting pharmacological properties.

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15. **2:** mp 107-109 °C, IR (neat, cm^{-1}) 3425 (OH), 1780 (CO); ^{1}NMR d (400 MHz, $CDCl_3$) 7.38-7.66 (m, 10H, $2xC_6H_5$), 4.46 (m, 2H, 3-H and 5-H), 4.22 (m, 1H, 4-H), 3.75 and 3.91 (m, 2H, 6-H_2), 1.05 (s, 9H, C $(CH_3)_3$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 174.0 (CO), 135.6, 135.4, 129.9, 127.8, 80.5, 74.8, 73.8, 61.6, 26.7, 19.2.
16. **6:** ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.80 (ddd, 1H, J_1=6.9 Hz, J2=10.5 Hz, J_3=17.4 Hz, 2-H), 5.30 (m, 2H, 1-H_2), 4.70 (m, 4H, 2x(OCH_2O) (MEM)), 4.60 (m, 1H, 4-H), 3.45-3.95 (m, 12H, 2x (OCH_2CH_2O) (MEM) and 3-H and 5-H and 6-H_2), 3.37 (s, 3H, OCH_3 (MEM)), 3.36 (s, 3H, OCH_3 (MEM)); ^{13}C NMR δ (100 MHz, $CDCl_3$) 134.8, 118.7, 97.4, 92.8, 81.4, 71.6, 71.5, 69.9, 69.8,

68.0, 67.3, 67.2, 63.2, 59.0.
17. **10:** IR (neat, cm^{-1}) 3300 (alkyne), ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.80 (ddd, 1H, J_1=6.9 Hz, J_2=10.5 Hz, J_3= 17.4 Hz, 2-H), 5.30 (m, 2H, 1-H2), 4.80 (m, 6H, 2x (OCH^2O) (MEM)), 4.23 (m, 1H, 4-H), 3.4-4.0 (m, 14H, 3x(OCH_2CH_2O) (MEM) and 3-H and 5-H), 3.36 (s, 9H, 3xOCH_3 (MEM)), 2.60 (m, 2H, 6-H_2), 1.95 (t, 1H, *J* =2.6 Hz, 8-H); MS (FAB) 315 (M^+-1, 100%).
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19. **12:** $[\alpha]_D^{25}$= – 92.5° (c=0.62, $CHCl_3$); UV λ_{max} (EtOH) 265 nm; ^{1}H NMR δ (400 MHz, $CDCl_3$) 6.36 (d, 1H, *J*= 11.2 Hz, 6-H), 6.02 (d, 1H, *J* =11.2 Hz, 7-H), 5.42 (m, 1H, 19-H), 5.08 (m, 1H, 19-H), 4.22 (m, 1H, 1-H), 4.15 (m, 1H, 3-H), 3.50 (m, 1H, 2-H), 3.04 (s, 1H, OH), 2.80 (dd, J_1=12.0 Hz, J_2=3.8 Hz, 1H, 9-H), 2.58 (S, 1H, OH), 2.48 (m, 2H, 4-H_2), 2.24 (s, 1H, OH), 0.91 (d, 3H, *J*= 6.3 Hz, 21-CH_3), 0.87 (d, *J* =l.7 Hz, 3H, 26-CH_3), 0.85 (d, *J* =1.7Hz, 3H, 27-CH_3), 0.54 (s, 3H, 18-CH_3).

Efficient Synthesis of Hydroxyethylidene and *(E)*- Alkene Dipeptide Isosteres

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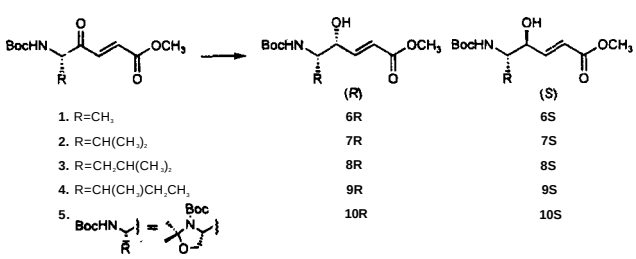
The development of novel dipeptide isosteres possesses a great value and importance in peptidomimetics. Among more than dozen peptide isosteres,[1] *(E)* -alkene dipeptide isostere[2] is a suitable amide bond surrogate in terms of mimicking the rigidity, bond angles, and bond length of the amide bond. We wish to report here general and efficient synthesis of hydroxyethylidene[3] and *(E)* -alkene dipeptide isosteres, which would considerably increase their application to drug and development.

Hydroxyethylidene dipeptide isostere first reported by Hanson *et al.* [3a] is an interesting dipeptide analog which combines conformational restriction, function as statine mimics, and the ability to undergo conjugate addition to enzyme nucleophiles such as cysteine thiol. Previous syntheses[3b,c,d] of hydroxyethylidene dipeptide isosteres mainly resorted to the Hansons method,[3a] which was hampered by the lack of Stereoselectivity in the vinylmagnesium halide addition to amino aldehydes, long reaction steps, and low overall yields. As a solution to the synthetic problem in preparing hydroxyethylidene dipeptide isosteres, we have developed an efficient route from ketovinyl dipeptide isostere.[4] Reduction of ketovinyl dipeptide isostere gives the corresponding hydroxyethylidene dipeptide isostere in one step (Scheme 1).

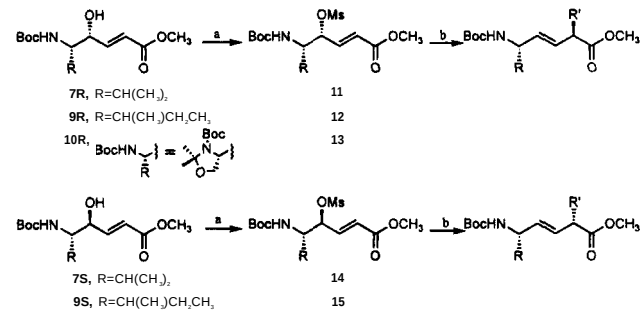
Various reducing agents including $NaBH_4$, $Zn(BH_4)_2$, $LiBEt_3H$, L-selectride, LS-selectride, $LiAl(i\text{-}Bu)_2(n\text{-}Bu)_2$, and $NaBH_3CN$ were used and additives such as Et_3BOMe, $ZnCl_3$, $CeCl_3$, and $SmCl_3$ were employed. Even though the Stereoselectivity of reduction was moderate (product ratio, *(R)* : *(S)* =88 : 12-18 : 82),[5] combined isolated yields of *(R)*- and *(S)*- alcohols were good to excellent (55-99%). Furthermore, by employing some additives ($CeCl_3$, $SmCl_3$) diastereoselectivity could be reversed and both diastereomers of hydroxyethyliene dipeptide isosteres could be prepared. Due to ease access of ketovinyl dipeptide isosteres from amino acids,[4] this synthetic route constitutes an efficient and general pathway for hydroxyethyliene dipeptide isosteres. Conversion of hydroxyethylidene to *(E)*- alkene dipeptide isosteres through γ-mesyloxy *(E)*- α,β-enoate intermediates was completed by using Ibuka's method.[3b]

Anti-S_N2' displacement of γ-mesyloxy leaving group with orgnocopper. BF_3 complex provided *(E)*- alkene dipeptide isostere in a stereoselective manner (Scheme 2). Experimental results are summarized in Table 1.

The salient features of this synthetic route for *(E)*- alkene dipeptide isosteres include: (1) the relatively few number of steps required, (2) excellent chemical yields and Stereoselectivity. Due to the simplicity and efficiency in preparation of scalemic γ-hydroxy α,β-enoates(hydroxyethylidene) and a



Scheme 1.



Scheme 2. Reagents and conditions: (a) MsCl, pyridine, CH_2Cl_2, 0 °C. (b) CuCN, R'MgCl, $BF_3 \cdot Et_2O$, THF, – 78 °C.