BULLETIN
OF THE
KOREAN CHEMICAL SOCIETY

VOLUME 18, NUMBER 5
MAY 20, 1997

BKCS 18(5) 459-562
ISSN 0253-2964

Communications

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

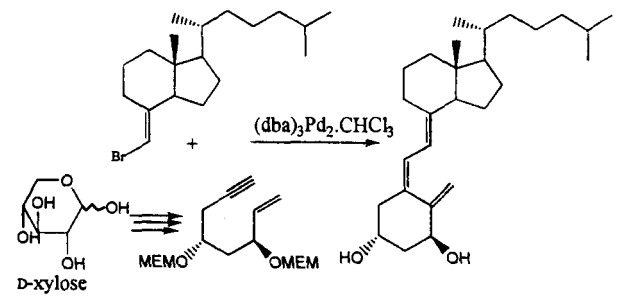
Joonggon Kim*[1], Robert M. Moriarty, and Doo Ok Jang [†]

Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60680
[†]Department of Chemistry, Yonsei University, Wonju 220-710, Korea
Received October 7, 1996

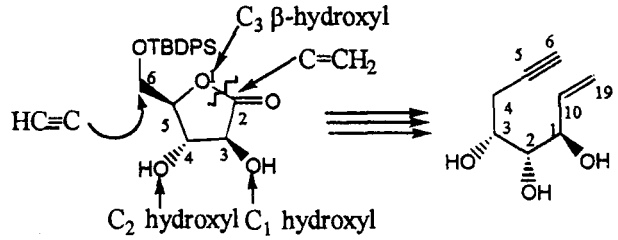
1α,25-Dihydroxyvitamin D_3, the hormonally active metabolite of Vitamin D_3, is associated with calcium homeostasis.[2] Its effect upon cellular differentiation and proliferation has been established.[3] Furthermore, members of this class of compounds show the possible connection between Vitamin D analogs 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.



2

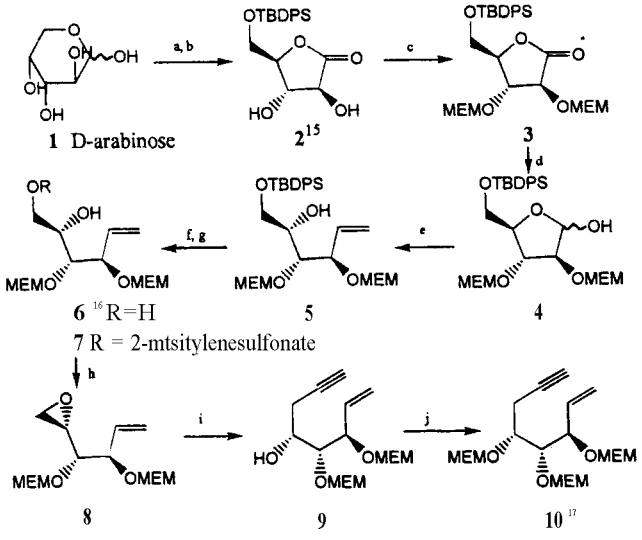
Scheme 2.

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_3 atom of the carbonyl group is ultimately the site of methylenation.

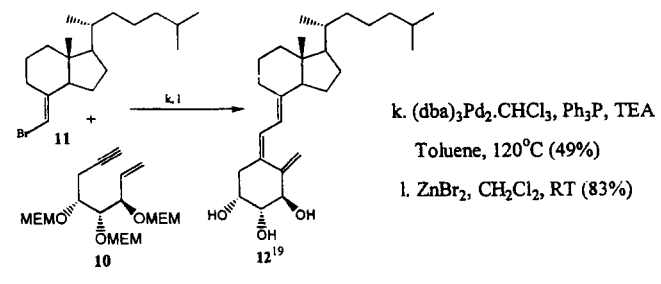
Synthesis of the 1,2,3-trihydroxy-1,7-enyne needed for 1α,2β-dihydroxyvitamin D_3 proceeded from D-arabinose **(1)** which was converted by known bromine oxidation[14] followed by selective protection of primary hydroxy group to (3*S*,4*R*,5*S*)-3,4-dihydroxy-5-[(*t*-butyldiphenylsiloxy)methyl]-2-tetrahydrofuranone **(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_3 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$_2$SiCl, imidazole, DMF, RT (a+b, 65%). [c]MEMCl, *i*-Pr$_2$NEt, CH_2Cl_2, Reflux (92%). [d]DIBAL, CH_2Cl_2, −65 °C (98%). [e]Ph$_3$PCH$_3$Br, *t*-BuOK THF, 0 °C (65%). [f] *n*-Bu$_4$NF, 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$_2$NEt, 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.

References

1. Current address: Hanwha Group Research & Engineering Center, Taejon 305-345, Korea.
2. Holick, M. F.; Semmler, E. J.; Schnoes, H. K.; DeLuca, H. F. *Science* **1973,** *180*, 190.
3. Tanaka, H.; Abe, E.; Miyaura, C.; Kuribayashi, T.; Konno, K.; Nishii, Y.; Suda, T. *Biochem. J.* **1982,** *204*, 713.
4. Smith, E. L.; Walworth, N. C.; Holick, M. F. *J. Invest. Dermatol.* **1986,** *86*, 709.
5. Mangelsdorf, D. J.; Koeffler, H. P.; Donaldson, C. A.; Pike, J. W.; Hanssler, M. R. *J. Cell. Biol.* **1984,** *99*, 391.
6. Provvedini, D. M.; Tsoukas, C. D.; Deftos, L. J.; Manolagas, S. C. *Science* **1983,** *221*, 1181.
7. Aloia, J. F. *Metabolism* **1990,** *39*, 35.
8. Dai, H.; Posner, G. H. *Synthesis* **1994,** 1383.
9. Muralidharan, K. R.; deLera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1993,** *58*, 1895.
10. Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992,** *114*, 9836.
11. Moriarty, R. M.; Kim, J.; Bruner, H. *Tetrahedron Lett.* **1995,** *36*, 51.
12. (a) Miyamoto, K.; Murayama, E.; Ochi, K.; Watanabe, H.; Kubodera, N. *Chem. Pharm. Bull.* **1993,** *41*, 1111. (b) Takahashi, T.; Nakazawa, M. *Synlett* **1993,** *37*. (c) Takahashi, T.; Nakazawa, M.; Sakamoto, Y.; Houk, K. N. *Tetrahedron Lett.* **1993,** *34*, 4075. (d) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994,** *59*, 7855. (e) One, Y.; Watanabe, H.; Kawase, A.; Kubodera, N. *Biorg. Med. Chem. Lett.* **1994,** *4*, 1523.
13. Moriarty, R. M.; Bruner, H. Tetrahedron Lett. **1995,** *36*, 9265.
14. Okabe, M.; Sun, R. C.; Zenchoff, G. B. *J. Org. Chem.* **1991,** *56*, 4392.
15. **2:** mp 107-109 °C, IR (neat, cm^{-1}) 3425 (OH), 1780 (CO); ^{1}NMR δ (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), ^1H 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%).
18. Miyamoto, K.; Kubodera, N.; Ochi, K.; Matsunaga, I.; Murayama, E. *Eur. Pat. Appl.* **1985**, EP 184,206.
19. **12:** $[\alpha]_D^{25}$ = – 92.5°(c=0.62, $CHCl_3$); UV λ_{max} (EtOH) 265 nm; ^1H 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=1.7 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

Byeang Hyean Kim* and Hye Jeong Ahn [1]

Department of Chemistry, Center for Biofunctional Molecules, Pohang University of Science and Technology, Pohang 790-784, Korea
Received December 17, 1996

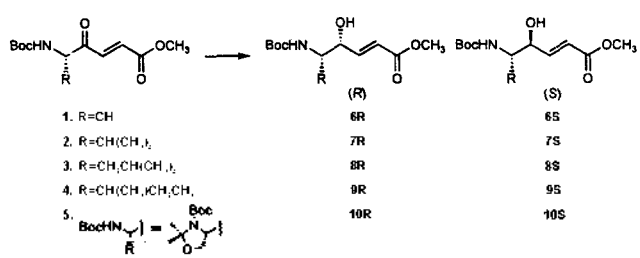
The development of novel dipeptide isosteres possesses a great value and importance in peptidomimetics. Among more than dozen peptide isosteres,[1] *(E)* -alkene dipeptide isostere[2] is a suitable amide bond surrogate in terms of mimicking the rigidity, bond angles, and bond length of the amide bond. 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).

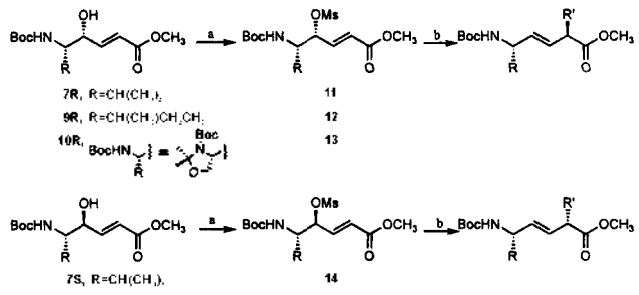
Various reducing agents including $NaBH_4$, $Zn(BH_4)_2$, LiBEt$_3$H, L-selectride, LS-selectride, LiAl(*i*- Bu)$_2$(*n*- Bu)$_2$, and $NaBH_3CN$ were used and additives such as Et_3BOMe, $ZnCl_2$, $CeCl_3$, and $SmCl_3$ were employed. Even though the Stereoselectivity of reduction was moderate (product 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-Et_2O, THF, – 78 °C.