Communications

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

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1α,25-Dihydroxyvitamin D₃, the hormonally active metabolite of Vitamin D₃, is associated with calcium homeostasis. Its effect upon cellular differentiation and proliferation has been established. Furthermore, members of this class of compounds show the possible connection between Vitamin D analogs and treatment of diseases, such as psoriasis or cancer and also the efficacy as immunomodulators. Its therapeutic use is limited by toxicity such as hypercalcemia. 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 possessing an appropriately substituted C₁₇ side chain and A ring analogs which have different stereochemistry in C₁ and C₃ position in A ring. Among the many A ring synthon routes a brilliant coupling method was achieved by Trost, et al. 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 D₃ (Scheme 1). Much recent attention to trifunctionalized A ring analogs 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- trihydroxyvitamin D₃ was reported by our group.

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 C₁ of the derived enyne is constant and β as in the natural vitamin D
series. The stereochemistry at C₁ and C₄ 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 C₁ of the tetrahydrofuranone and the C₄ atom of the carbonyl group is ultimately the site of methylation.

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

Diol protection of 2 with MEMCl, DIBAL reduction, methylation, and deprotection of the C₃ hydroxy group gave compound 6. Selective mesitylenesulfonylation of the C₁ hydroxy group with sterically hindered mesitylenesulfonyl chloride, intramolecular epoxide formation, regioselective addition of acetylide anion, and protection of hydroxy group yielded the synthesis of 1,7-enyne (10). Coupling of 10 with 7-(2)-bromo-des-AB-cholest-7-ene (11) according to the Trost procedure followed by deprotection with ZnBr₂, yielded 1α,2β-dihydroxyvitamin D (12), whose spectroscopic data were in accordance with those reported previously (Scheme 4).

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 of 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

15. 2: mp 107-109 °C, IR (neat, cm⁻¹) 3425 (OH), 1780 (CO); 'H NMR δ (400 MHz, CDCl₃) 7.38-7.66 (m, 10H, 2xCH₃), 4.46 (m, 2H, 3-H and 5-H), 4.22 (m, 1H, 4-H), 3.75 and 3.91 (m, 2H, 6-H), 1.05 (s, 9H, C₅H₃). 'C NMR δ (100 MHz, CDCl₃) 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: 'H NMR δ (400 MHz, CDCl₃) 5.80 (ddd, 1H, J=6.5, 12.9, 17.4 Hz), 3.75 (m, 2H, 1-H), 4.70 (m, 4H, 2x(OCH₃) (MEM)), 4.60 (m, 1H, 4-H), 3.45-3.95 (m, 12H, 2x (OCH₃) (MEM) and 3-H and 5-H), 3.37 (s, 3H, OCH₃ (MEM)), 3.36 (s, 3H, OCH₃ (MEM)); 'C NMR δ (100 MHz, CDCl₃) 134.8, 118.7, 97.4, 92.8, 81.4, 71.6, 71.5, 69.9, 69.8,
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, (E)-alkene dipeptide isosteres 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 and (E)-alkene dipeptide isosteres, which would considerably increase their application to drug and development.

Hydroxyethylidene dipeptide isostere first reported by Hanson et al. 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 of hydroxyethylidene dipeptide isosteres mainly resorted to the Hansons method, 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. Reduction of ketovinyl dipeptide isostere gives the corresponding hydroxyethylidene dipeptide isostere in one step (Scheme 1).

Various reducing agents including NaBH₄, Zn(BH₄)₂, LiBEt₃H, L-selectride, LS-selectride, LiAl(H–Bu)(n–Bu), and NaBH₃CN were used and additives such as Et₂BOMe, ZnCl₂, CeCl₃, and SmCl₃ were employed. Even though the Stereoselectivity of reduction was moderate (product ratio, (R) : (S) = 88 : 12 : 18 : 82), combined isolated yields of (R)- and (S)- alcohols were good to excellent (55-99%). Furthermore, by employing some additives (CeCl₃, SmCl₃) diastereoselectivity could be reversed and both diastereomers of hydroxyethylidene dipeptide isosteres could be prepared. Due to ease access of ketovinyl dipeptide isosteres from amino acids, this synthetic route constitutes an efficient and general pathway for hydroxyethylidene dipeptide isosteres.

Conversion of hydroxyethylidene to (E)-alkene dipeptide isosteres through γ-mesyloxy (E)-α,β-enoates intermediates was completed by using Ibuka’s method. Anti-S₂’ displacement of γ-mesyloxy (E)-α,β-enoate isostere was carried out by using orgnocopper. BF, 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

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17. 10: IR (neat, cm⁻¹) 3300 (alkyne), ¹H NMR δ (400 MHz, CDCl₃) 5.80 (dd, 1H, J = 6.9 Hz, J = 17.4 Hz, 2-H), 5.30 (m, 2H, 1-H₂), 4.80 (m, 6H, 2x (OCH₂O) (MEM)), 4.23 (m, 1H, 4-H), 3.4-4.0 (m, 14H, 3x(OCH₂CH₂O) (MEM) and 3-H and 5-H), 3.36 (s, 9H, 3xOCH₂ (MEM)), 2.60 (m, 2H, 6-H₂), 1.95 (t, 1H, J = 2.6 Hz, 8-H); MS (FAB) 315 (M+1, 100%).


19. 12: [α]D = - 92.5° (c=0.62, CHCl₃); UV λmax (EtOH) 265 nm; ¹H NMR δ (400 MHz, CDCl₃) 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 = 12.0 Hz, J = 3.8 Hz, 1H, 9-H), 2.58 (S, 1H, OH), 2.48 (m, 2H, 4-H), 2.24 (s, 1H, OH), 0.91 (d, 3H, J = 6.3 Hz, 21-CH), 0.87 (d, J = 1.7 Hz, 3H, 26-CH), 0.85 (d, J = 1.7 Hz, 3H, 27-CH), 0.54 (s, 3H, 18-CH).

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Scheme 1

Scheme 2. Reagents and conditions: (a) MsCl, pyridine, CH₂Cl₂, 0 °C. (b) CuCN, R'MgCl, BF₃, Et₂O, THF, -78 °C.