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Stereoselective Synthesis of 1α-Hydroxyvitamin D_3 A-Ring Synthons by Palladium-Catalyzed Cyclization

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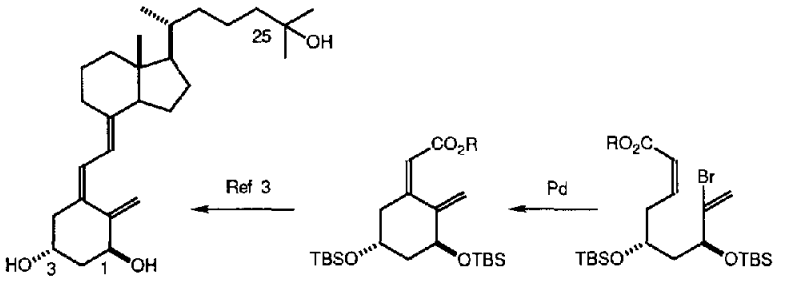
Abstract: Palladium-catalyzed cyclization of 8-bromo-2,8-nonadienoates proceeded stereoselectively to give 1α-hydroxyvitamin D_3 A-ring synthons in good yields.

1α,25-Dihydroxyvitamin D_3 is known as the hormonally active form of vitamin D_3. Recently this hormone was found to induce cell differentiation of myeloid leukemia cells in addition to the role in calcium regulation.[1] Since these potent biologically activities, a lot of synthetic efforts for 1α,25-dihydroxyvitamin D_3 have been made.[2] On the basis of Lythgoe's synthesis of vitamin D_3, Hoffman la Roche's group achieved the synthesis of 1α,25-dihydroxyvitamin D_3 using **2e** as a useful precursor of A-ring synthon.[3] So far several synthetic methods for A-ring synthons starting from readily available chiral cyclohexanes have been reported,[4] but cyclization of acyclic compound has scarcely been reported. The latter has potent possibility to obtain various A-ring derivatives, because acyclic compounds are easily accessible. For our interest of structure-activity relationships,[5] especially the effect of stereochemistry at C1 and C3 of 1α-hydroxyvitamin D_3, the synthesis of A-ring synthon and its derivatives has been investigated. In this paper we wish to report a facile and stereoselective syntheses of **2a-2d** using the palladium-catalyzed intramolecular cyclization.[6]

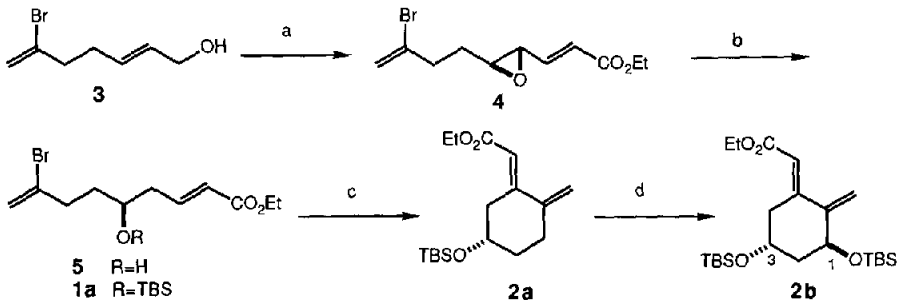


1α,25-Dihydroxyvitamin D_3 **2e** **1e**

The key intermediate (*E*)-8-bromo-2,8-nonadienoate **1a** for the optically active **2a** was prepared from the allylic alcohol **3** in 5 steps (**Scheme 1**). Sharpless asymmetric epoxidation of **3** followed by Swern oxidation and subsequent Horner-Emmons reaction gave the (*E*)-α,β-unsaturated epoxy ester **4** in 61% yield from **3**. The epoxy group of **4** was reduced regioselectively by the palladium-catalyzed hydrogenolysis with formic acid[7] to give the optically active alcohol (5S)-5[8] whose hydroxy group was protected as silyl ether to

give **1a** in 87% yield from **4**. Cyclization of **1a** to **2a** was carried out using 5 mol% of $Pd(OAc)_2$-PPh_3(1:2) and K_2CO_3 (2 eq) in CH_3CN under reflux for 18 h[9] in 66% yield. 1α-Hydroxy group of **2b** was introduced using SeO_2[10] followed by silylation of the alcohol to give **2b**[11] in 29% yield. Because of unsatisfactory result of the conversion **2a** to **2b**, 1-hydroxy group was introduced before cyclization. Thus, the disiloxy ester

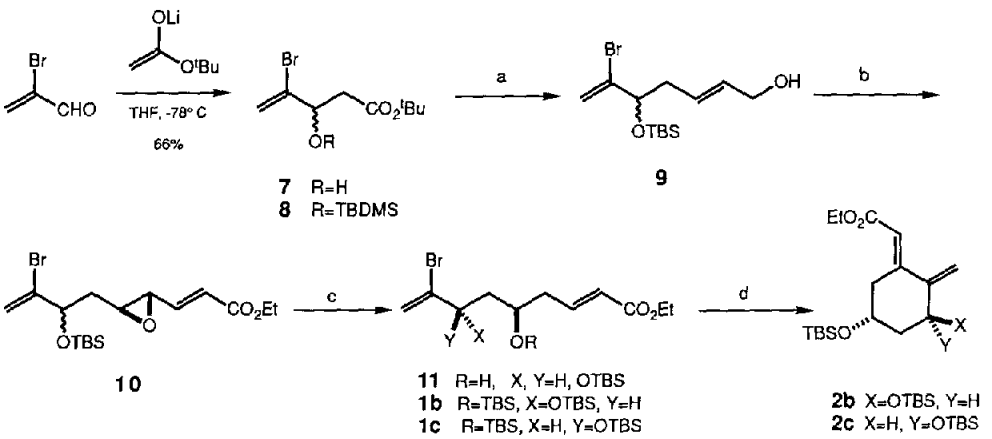
Scheme 1



(a) (1) (+)-DET, $Ti(O^iPr)_4$, TBHP, -23°C, (2) $(COCl)_2$, DMSO, Et_3N, -78°C, (3) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0°C, 61% overall; (b) (1) 5 mol% $Pd_2(dba)_3CHCl_3$, 5 mol% n-Bu_3P, 5 eq of HCO_2H, 2 eq of Et_3N, dioxane, rt, (2) *t*-$BuMe_2SiCl$, imidazole, DMF, 87% overall; (c) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 2 eq of K_2CO_3, CH_3CN, reflux, 66%; (d) (1) 0.7 eq of SeO_2, 4 eq of NMO, MeOH-CH_2Cl_2, (2) *t*-$BuMe_2SiCl$, imidazole, DMF, 29% overall.

1b was prepared from α-bromoacrolein as shown in **Scheme 2**. Reaction of α-bromoacrolein with lithium enolate of *tert*-butyl acetate gave the hydroxy ester **7** in 66% yield. After protecting the hydroxy group as silyl ether, DIBAH reduction of **8** followed by Horner-Emmons reaction and subsequent reduction of ester group

Scheme 2

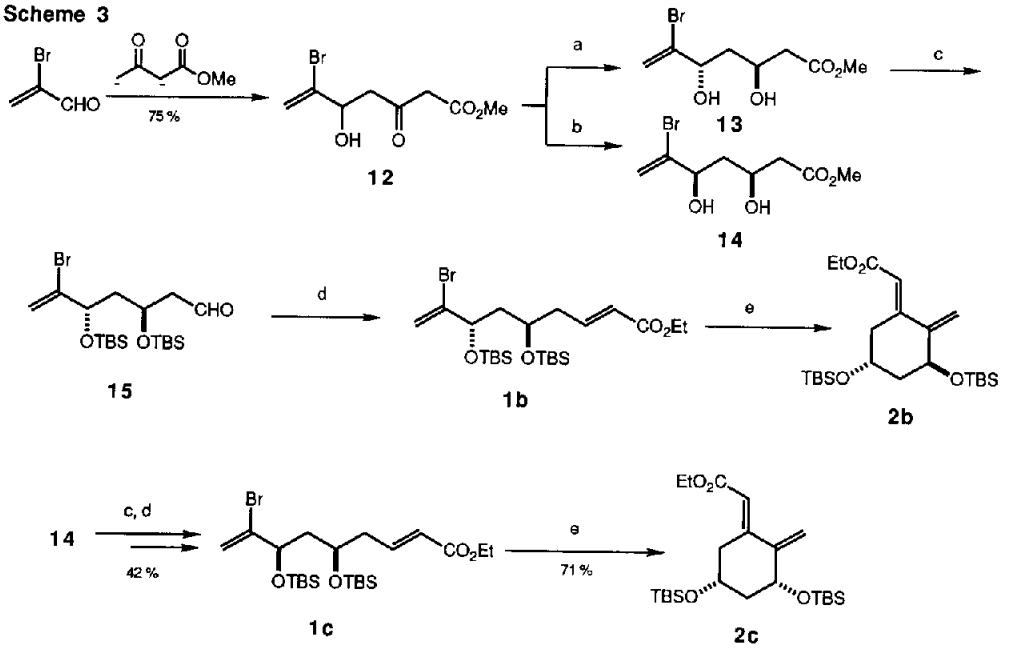


(a) (1) *t*-$BuMe_2SiCl$, imidazole, DMF, (2) 1.2 eq of DIBAH, toluene, -78°C, (3) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0°C, (4) DIBAH, toluene, -78°C, 53% overall; (b) (1) (+)-DET, $Ti(O^iPr)_4$, TBHP, -23°C, (2) $(COCl)_2$, DMSO, Et_3N, -78°C, (3) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0°C, 70% overall; (c) (1) 5 mol% $Pd_2(dba)_3CHCl_3$, 5 mol% n-Bu_3P, 5 eq of HCO_2H, 2 eq of Et_3N, dioxane, rt, 73%, (2) *t*-$BuMe_2SiCl$, imidazole, DMF, 92%; (d) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 2 eq of K_2CO_3, CH_3CN reflux, 90%.

gave the allylic alcohol **9** in 53% yield from **7**. The allylic alcohol **9** was converted to the esters a diastereo mixture of (5R, 7S) and (5R, 7R)-**11** by a similar procedure as **3** to **5** in 51% yield (4 steps). As protecting the hydroxy group as silyl ether (92% yield), the mixture of **1b** and **1c** was subjected to the cyclization to give a mixture of **2b** and **2c** (1:1) in 90% yield, which were separated by column chromatography on silica gel.

Stereoselective 1,3-*syn* or 1,3-*anti* alcohols were prepared by reduction of β-hydroxyketone using Et_3B-$NaBH_4$[12] or $Me_4NBH(OAc)_3$[13] respectively. Reaction of α-bromoacrolein with the dianion prepared from methyl acetoacetate (75% yield) followed by reduction with $Me_4NBH(OAc)_3$ gave the 1,3-*anti* diol **13** in 75% yield. After silylation of the hydroxy groups, the ester was reduced with DIBAH to give the aldehyde **15** in 72% yield (2 steps). Reaction of **15** with $(EtO)_2P(=O)CH_2CO_2Et$ gave the (*E*)-α,β-unsaturated ester **1b** in 80% yield. The cyclization of **1b** to **2b** was carried out in 86% yield. Similarly 1,3-*syn* disilyloxy ester **1c** which was prepared by reduction of **12** with Et_3B-$NaBH_4$ (56% yield) cyclized to give **2c**[11] in 71% yield (**Scheme 3**).

Scheme 3



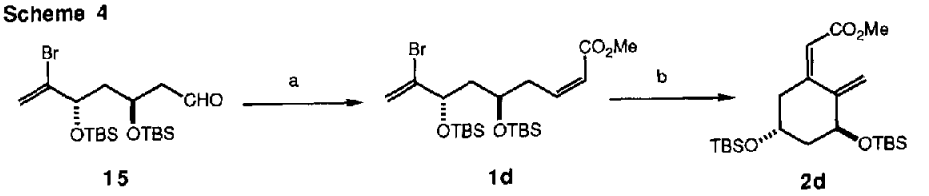
(a) $Mc_4NBH(OAc)_3$, CH_3CN, 0°C, 75%; (b) Et_3B, $NaBH_4$, MeOH-THF, -78°C, 58%; (c) (1) *t*-$BuMe_2SiCl$, DMF, imidazole, (2) DIBAH, toluene, -78°C, 72% overall; (d) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0°C, 80%; (e) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 2 eq of K_2CO_3, CH_3CN reflux, 86%.

As described as above, cyclization of (*E*)-unsaturated esters gave (*E*)-exodienes stereoselectively. These stereochemical outcome is explained by the well known *cis* addition and *syn* elimination mechanism of Heck reaction,[14] which implied us that (*Z*)-exocyclic diene could be obtained by cyclization of (*Z*)-dienyl ester. The (*Z*)-α,β-unsaturated ester **1d** was prepared by (*Z*)-olefination[15] of **15**. The ester **1d** was cyclized to give **2d**[11] in 90% yield without formation of *E* isomer (**Scheme 4**).

The palladium-catalyzed cyclization is stereoselective and the method described here is useful and ap-

plicable to other various type of A-ring synthons. Total synthesis of 1α,25-dihydroxyvitamin D_3 based on this methodology is now in progress.

Scheme 4



15 **1d** **2d**

(a) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, -78°C, 68%; (b) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 2 eq of K_2CO_3, CH_3CN reflux, 90%.

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11. ^1H NMR (400 MHz, $CDCl_3$)
    2b: δ 5.94 (s, 1H), 5.17 (s, 1H), 5.11 (s, 1H), 4.57 (m, 1H), 4.22 (m, 1H).
    2c: δ 5.91 (s, 1H), 5.18 (s, 1H), 5.13 (s, 1H), 4.07 (m, 1H), 4.05 (ddd, *J*=13.3, 4.5, 1.9 Hz, 1H).
    2d: δ 5.63 (s, 1H), 5.19 (s, 1H), 4.99 (s, 1H), 4.55 (m, 1H), 4.25 (m, 1H).
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