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CONVERGENT AND STEREOSELECTIVE SYNTHESIS OF VITAMIN D_3 VIA 3,5-CYCLOVITAMINS D_3

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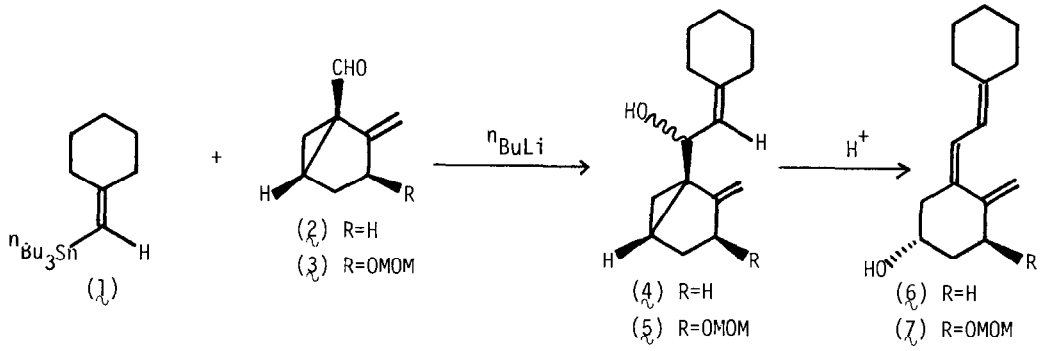
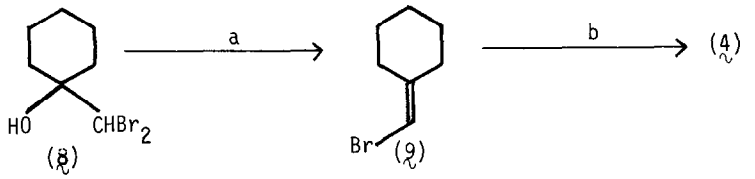
Summary: A convergent and stereoselective synthesis of vitamin D_3 was achieved via 3,5-cyclovitamins D_3 (20) which were prepared from the chiral aldehyde (2) and the vinyl bromide (12) derived from Grundmann's ketone.

In the previous paper[1], we reported a high stereocontrolled synthesis of the model compounds (6 and 7) of vitamin D_3 and its 1α-hydroxy derivative from the cyclo compounds (4 and 5) which were prepared by the coupling reaction of organostannane (1) and (±)-aldehydes (2 and 3). By the application of this strategy, a convergent and stereoselective synthesis of vitamin D_3 was achieved as reported in this communication.

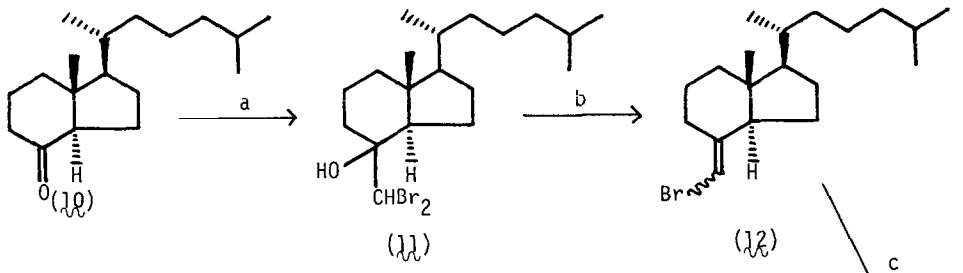


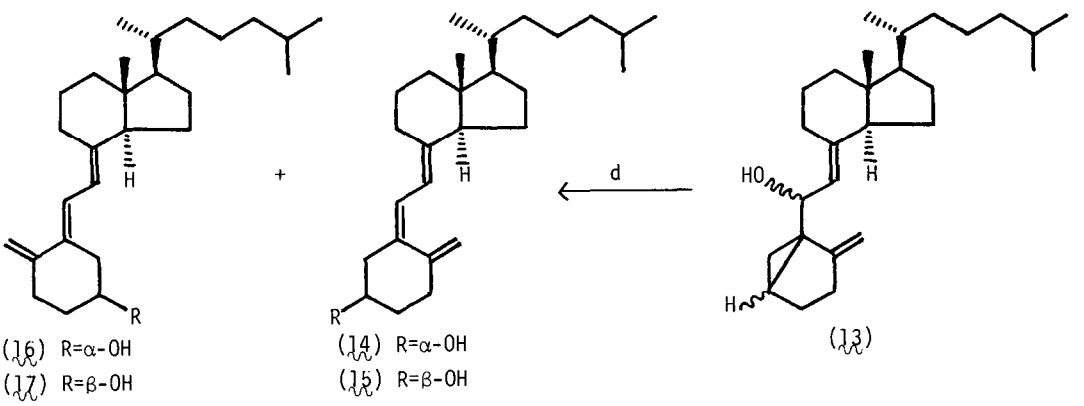
Since the preparation of the corresponding organostannane from Grundmann's ketone (10)[2] was tedious, we firstly investigated the crucial coupling reaction by the alternative method. Thus the dibromide (8)[3] was reduced with zinc and acetic acid in CH_2Cl_2[4] to give cyclohexylidene bromide (9)[5] in 83.5% yield. The metallation[4] of 9 using two equivalents of t-butyllithium at -78°C in THF followed by condensation with the (±)-aldehyde (2) at -78°C afforded in 79.2% yield an epimeric mixture of the alcohols (4), which was identical with the previous sample.[1] Therefore optically active Grundmann's ketone (10)[2] was

reacted with dibromomethane in the presence of lithium dicyclohexylamide (LDCA)[3] in THF at -98°C to give in 43.3% yield the dibromide (11)[5] which was subjected to the reduction with zinc and acetic acid.[4] The vinyl bromide (12)[5] obtained in 89% yield as a mixture of two isomers in a ratio of 1 : 0.9 was metallated and coupled with the racemate of the aldehyde (2) under the same reaction conditions as above to produce the alcohols (13)[5] in 55% yield as a mixture of stereoisomers. Solvolysis[6] of the stereoisomeric mixture of 13 in the presence of p-toluenesulfonic acid in aqueous dioxane at 55°C for 10 min followed by silica gel column chromatography gave two substances. The spectral data of the less polar product (13% yield) were superimposable on those of trans-vitamin D_3



a: Zn, AcOH. b: ^{t}BuLi; (±)-2, THF, -78°C.

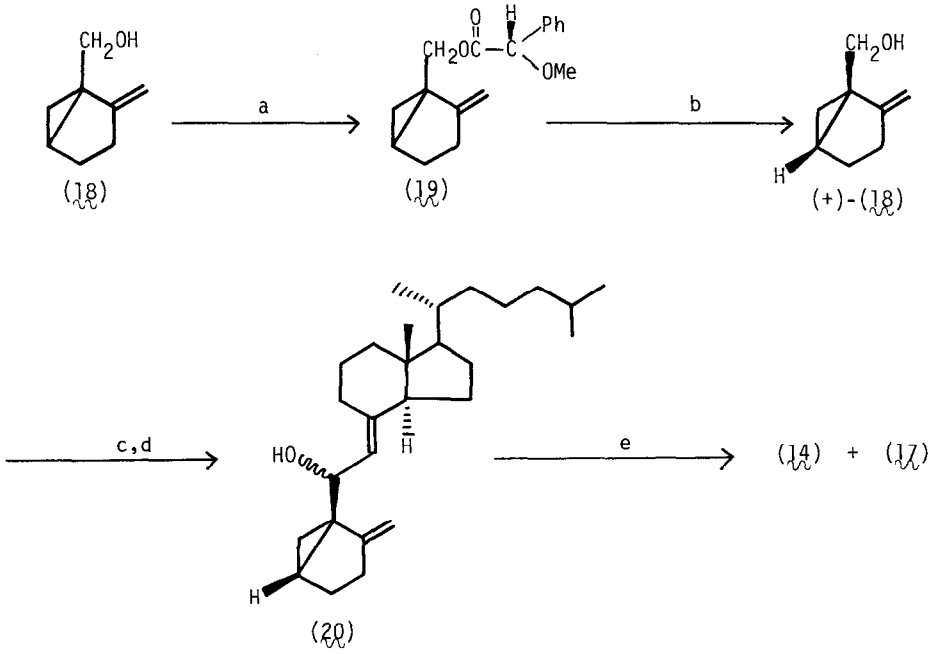




a: CH_2Br_2, LDCA, -98°C. b: Zn, AcOH. c: ^{t}BuLi; (±)-2. d: p-TsOH, aq. dioxane.

while those of the polar product (35.3% yield) was very similar to those of vitamin D_3. However HPLC of the latter using Hitachi gel 3011 eluting with MeOH - $CHCl_3$ (4 : 1 v/v) revealed that the product was a 1 : 1 mixture of two epimers (14 and 15) at the chiral C_3 position. Therefore the former product must be also a mixture of two epimers (16 and 17). On the basis of the above result, we then investigated a stereoselective synthesis of vitamin D_3 starting from the chiral aldehyde (2).

The 1-hydroxymethyl-2-methylenebicyclo[3.1.0]hexane (18) was reacted with S-(+)-O-methylmandelic acid in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine[7] to give, in 95.5% yield, the diastereoisomeric mixture of the esters (19)[5], whose separation was accomplished by HPLC using LiChrosorb SI 60 eluting with AcOEt - n-hexane (1 : 49 v/v). Two ester fractions were respectively hydrolyzed with potassium hydroxide in methanol to afford quantitatively the alcohols[5], $[\alpha]_D^{20}$ +45.0° (c=0.44, n-hexane) and $[\alpha]_D^{20}$ -46.5° (c= 0.46, n-hexane). The (+)-isomer (18), whose absolute configuration was determined by the conversion to vitamin D_3, was oxidized with pyridinium chlorochromate to the corresponding aldehyde, which was coupled with the bromide (12) as before. The 3,5-cyclovitamins D_3 (20) obtained in 46.5% yield were separated into two components[5] by silica gel column chromatography. The solvolysis of the polar compound (26% yield) as above gave vitamin D_3 (14), $[\alpha]_D^{20}$ +50.5° (c=0.27, $CHCl_3$), mp 83 - 86°C [lit.[9], $[\alpha]_D$ +51.9° ($CHCl_3$), mp 84 - 85°C] in 54.8% yield, which was identical with the authentic compound in all re-



a: S-(+)-O-methylmandelic acid, DCC, DMAP. b: KOH, MeOH. c: PCC.
d: 12, ^tBuLi. e: p-TsOH, aq. dioxane.

spects. Formation of the trans-isomer (17) was not detected by TLC analysis[8]. On the other hand, the less polar compound furnished, on the same reaction, vitamin D_3 (14), $[\alpha]_D^{20}$ +50.8° (c=0.43, $CHCl_3$) in 23.8% yield and trans-vitamin D_3 (17), $[\alpha]_D^{20}$ +119.4° (c=0.27, $CHCl_3$) in 19.2% yield. Thus a stereoselective synthesis of vitamin D_3 was accomplished. Since it was made clear from the previous works[1,10] that the cleavage of the cyclopropane ring proceeded through the inversion of stereochemistry, the absolute configuration of the (+)-alcohol (18) was determined as shown.

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References and Notes

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5) All new compounds have been fully characterized by IR ($CHCl_3$), NMR and mass spectra and elemental analysis and/or high resolution mass spectrometry. (9): NMR (CCl_4) δ 5.71 (1H, s, >C=CHBr). (11) NMR (CCl_4) δ 5.61 (1H, s, $-CHBr_2$). (12):NMR (CCl_4) δ 5.56 (0.53H, s, >C=CHBr), 5.86 (0.47H, s, >C=CHBr). (13) less polar compound: NMR δ 0.58 (3H, s, 18-Me); MS m/e 384 (M^+). polar compound: NMR δ 0.53 (3H, s, 18-Me); MS m/e 384 (M^+). (19) less polar compound: NMR ($CDCl_3$) δ 3.40 (3H, s, OMe), 4.22 and 4.36 (each 1H, each d, J = 12 Hz, OCH_2), 4.72 - 4.76 (3H, m, $=CH_2$, CHOMe). polar compound: NMR ($CDCl_3$) δ 3.39 (3H, s, OMe), 4.19 and 4.34 (each 1H, each d, J = 12 Hz, OCH_2), 4.64 - 4.76 (3H, m, $=CH_2$, CHOMe).
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8) Sheves and Mazur[6] examined the solvolysis of two epimers of 3,5-cyclovitamins D_3 and they reported the formation of trans-isomer (17) along with vitamin D_3 from both compounds.
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