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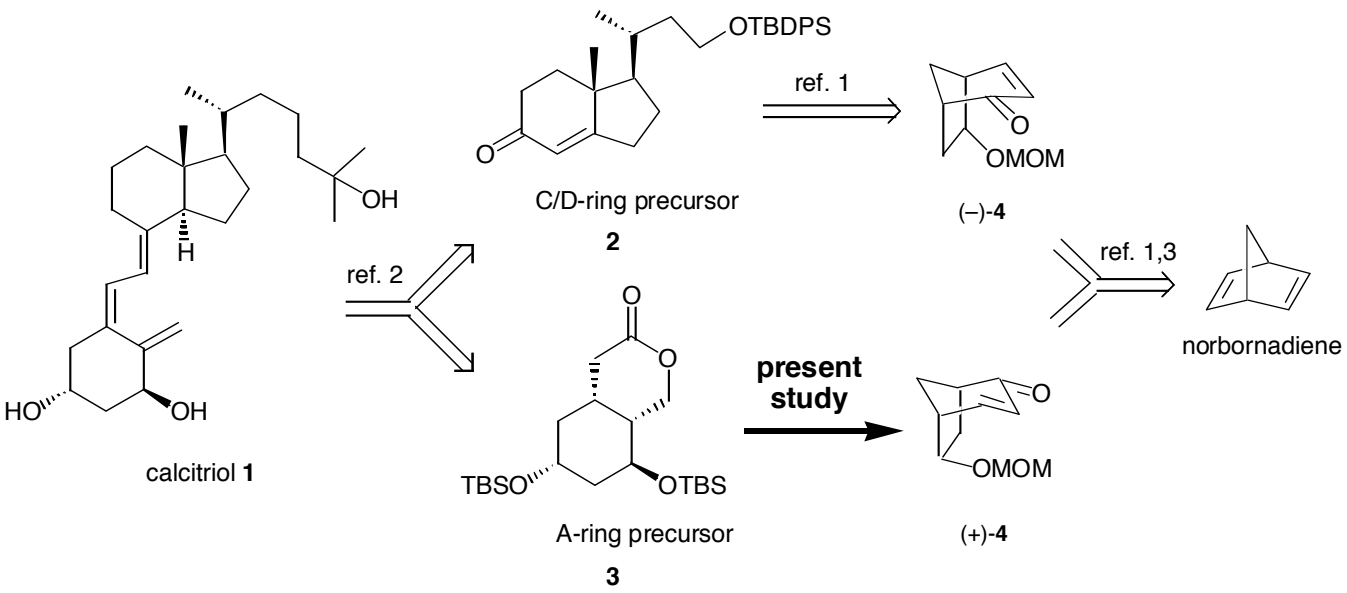
A NEW ROUTE TO THE CALCITRIOL A-RING PRECURSOR USING A BICYCLO[3.2.1]OCTANE CHIRAL BUILDING BLOCK

Norio Miyazawa, Ayako Tosaka, Keisuke Hanada, and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan; E-mail: konol@mail.cc.tohoku.ac.jp

Abstract – A concise route to the A-ring precursor of calcitriol (1α,25-dihydroxyvitamin D_3) has been developed starting from the chiral building block having a bicyclo[3.2.1]octane framework. Since we have already developed a diastereocontrolled synthesis of the C/D-ring precursor starting with the enantiomeric chiral building block, the present synthesis implies the total synthesis of calcitriol from a single precursor in a formal sense.

We have recently developed[1] an enantio- and diastereocontrolled route to the C/D-ring precursor (**2**) of calcitriol[2] (1α,25-dihydroxyvitamin D_3) (**1**), an important hormonal substance in human physiology, starting with the chiral building block ((–)-**4**) having a bicyclo[3.2.1]octane framework. We also prepared the chiral building block ((–)-**4**), with its enantiomer ((+)-**4**), starting from norbornadiene by a route involving either an enzymatic[3] or a chemical[1] resolution step. Because of its inherent stereochemical and chemical nature with a sterically biased structure containing two oxygen functionalities, it serves as a versatile chiral building block and has already been used in the efficient stereocontrolled syntheses of the antibiotic diterpene (+)-ferruginol,[3] the analgesic alkaloid (–)-morphine,[4a] antitumor sesquiterpene (+)-vernolepin[4b] and a yohimbinoid indole alkaloid key building block 18-yohimbone[4c] in addition to the calcitriol C/D-ring precursor (**2**).[1] We have now attempted the diastereocontrolled construction of the calcitriol A-ring precursor **3**[5] utilizing the same chiral building block (**4**), the enantiomer of which was used for the synthesis[1] of the C/D-ring precursor (**2**), to establish a convergent route to calcitriol (**1**) and to extend the versatility of the chiral building block. We report here a diastereocontrolled route leading to the A- ring precursor (**3**)[2,6,7] of calcitriol (**1**)[2] starting with the building block ((+)-**4**) thus completing the total synthesis of calcitriol (**1**) from a single source in a formal sense (**Scheme 1**).

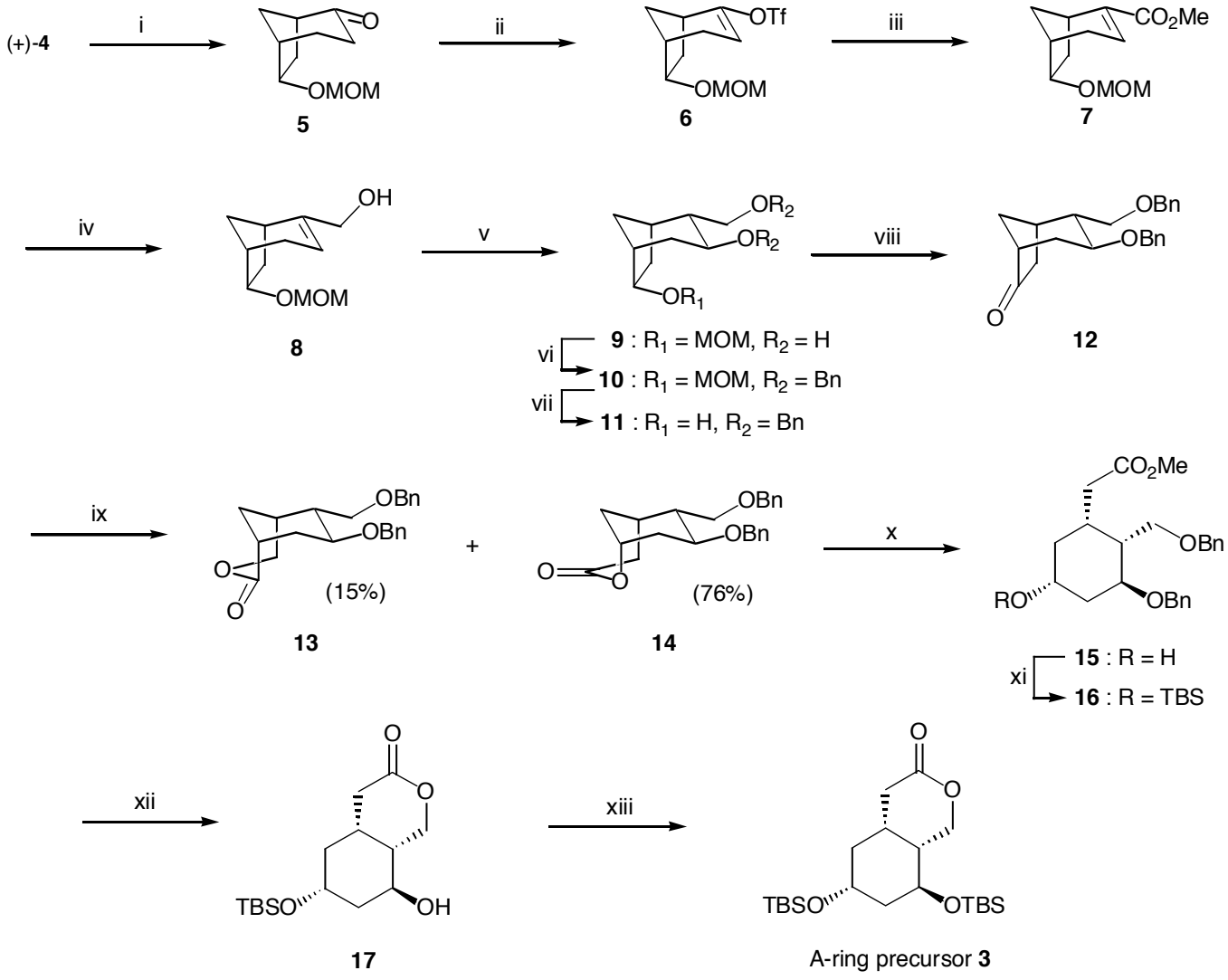


Scheme 1

The enone ((+)-**4**) (>99% ee by CHIRALCEL OD, elution with *i*-PrOH-hexane 1:99) was first converted into the ketone (**5**), $[\alpha]_D^{26}$ +113.5° (*c* 1.0, $CHCl_3$), by catalytic hydrogenation. The ketone (**5**) was treated with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]pyridine (Comins' reagent)[8] in the presence of sodium hexamethyldisilazide to give the triflate (**6**) which was exposed to carbon monoxide in DMF containing methanol in the presence of palladium (II) acetate and triphenylphosphine[9] to furnish the α,β-unsaturated ester (**7**), $[\alpha]_D^{27}$ –18.5° (*c* 1.0, $CHCl_3$). The ester (**7**) was reduced with diisobutylaluminum hydride (DIBAL) to give the allyl alcohol (**8**), $[\alpha]_D^{24}$ +14.1° (*c* 1.0, $CHCl_3$). Without protection the alcohol (**8**) was directly treated with borane-dimethyl sulfide complex in THF to give diastereoselectively the diol (**9**), $[\alpha]_D^{28}$ +47.1° (*c* 1.0, $CHCl_3$), as a single product after exposure to alkaline hydrogen peroxide. Owing to the inherent convex-face selectivity of the bicyclo[3.2.1]octane framework, the diol (**9**) allowed diastereoselective introduction of the secondary hydroxy functionality with the requisite β-stereochemistry. After benzylation, the resulting dibenzyl ether (**10**), $[\alpha]_D^{28}$ +93.1° (*c* 1.1, $CHCl_3$), was treated with saturated methanolic hydrogen chloride[10] to remove the MOM-protecting group generating the secondary alcohol (**11**), $[\alpha]_D^{23}$ +88.5° (*c* 1.0, $CHCl_3$). On oxidation with pyridinium chlorochromate (PCC), the alcohol (**11**) gave the ketone (**12**), $[\alpha]_D^{25}$ +50.2° (*c* 1.1, $CHCl_3$). The overall yield of the ketone (**12**) from the chiral building block ((+)-**4**) was 54% in eight steps.

Having introduced diastereoselectively one of the two requisite secondary oxygen functionalities on the cyclohexane ring, the introduction of the remaining functionality on the face opposite the first one was

next carried out by employing the Baeyer-Villiger oxidation. Although treatment of the ketone (**12**) with *m*-chloroperbenzoic acid did not proceed with complete regioselectivity, the desired lactone (**14**), mp 78-79 °C, $[\alpha]_D^{24}$ +51.6° (*c* 1.0, $CHCl_3$), was obtained in 76% yield with a 15% yield of the readily separable regioisomeric by-product (**13**), $[\alpha]_D^{24}$ +90.3° (*c* 0.2, $CHCl_3$), after separation by silica gel column chromatography. The major product (**14**) was refluxed with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the methyl ester (**15**) which was immediately used for the next conversion.



Scheme 2: i, H_2, 10% Pd-C, AcOEt (96%). ii, $NaN(SiMe_3)_2$, Comins' reagent, THF, –78 ºC. iii, CO, MeOH, Et_3N, $Pd(OAc)_2$, DMF (84%, 2 steps). iv, DIBAL, CH_2Cl_2 (96%). v, BH_3-Me_2S, THF, then 30% H_2O_2, aq. 10% NaOH (98%). vi, BnBr, Bu_4NI, NaH, THF (85%). vii, HCl-MeOH (96%). viii, PCC, CH_2Cl_2 (88%). ix, *m*-CPBA, CH_2Cl_2. x, *p*-TsOH (cat.), MeOH, reflux. xi, TBS-OTf, Et_3N, CH_2Cl_2 (91%, 2 steps). xii, H_2, 10% Pd-C, AcOEt then toluene, reflux (84%, 2 steps). xiii, TBS-Cl, imidazole, DMF (84%).

After *O*-silylation of **15**, the silyl ether (**16**), $[\square]_D^{23}$ –2.5° (*c* 0.9, $CHCl_3$), obtained was sequentially debenzylated under hydrogenolysis conditions and refluxed in toluene to afford the bicyclic lactone (**17**), mp 93- 94 °C, $[\square]_D^{24}$ +37.6° (*c* 0.6, $CHCl_3$). Finally, the secondary hydroxy functionality on the lactone (**17**) was silylated to give the A-ring precursor **(3)**,[11] mp 76- 78 °C, $[\square]_D^{24}$ +22.3° (*c* 0.9, $CHCl_3$). The overall yield of (**3**) from the ketone intermediate (**12**) was 49% in five steps (**Scheme 2**).

In summary, we have obtained the A-ring precursor (**3**) of calcitriol (**1**) starting with our bicyclo[3.2.1]octane building block ((+)-**4**) in 26% overall yield in 13 steps. Since we have already established a stereocontrolled synthesis of the C/D-ring precursor (**2**) starting from the enantiomeric building block ((–)-**4**), a convergent route to calcitriol (**1**) has now been established in a formal sense.

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11. Physical and spectroscopic data of the A-ring precursor (**3**) are not given in the previous synthesis:[5] mp 76 - 78 °C. $[\alpha]_D^{24}$ +22.3° (c 0.9, $CHCl_3$). IR (film): ν = 1740. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (br s, 12H), 0.85 (br s, 18H), 1.52 – 1.79 (m, 5H), 2.39 – 2.44 (m, 1H), 2.52 (dd, J = 6.9, 18.4 Hz, 1H), 2.98 (dd, J = 8.2, 18.4 Hz, 1H), 4.00 (td, J = 3.6, 8.2 Hz, 1H), 4.08 – 4.17 (m, 2H), 4.49 (dd, J = 5.4, 11.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, 18.0, 25.7, 29.5, 34.3, 36.2, 40.8, 41.7, 64.3, 68.1, 68.6, 171.1. MS: m/z = 357 (M^+–Bu^t). HRMS: m/z = $C_{17}H_{33}O_4Si_2$: Calcd = 357.1675. Found = 357.1900.