Concise Enantiocontrolled Synthesis of the *A*-Ring Precursor of Calcitriol from the Chiral Cyclohexadienone Synthon

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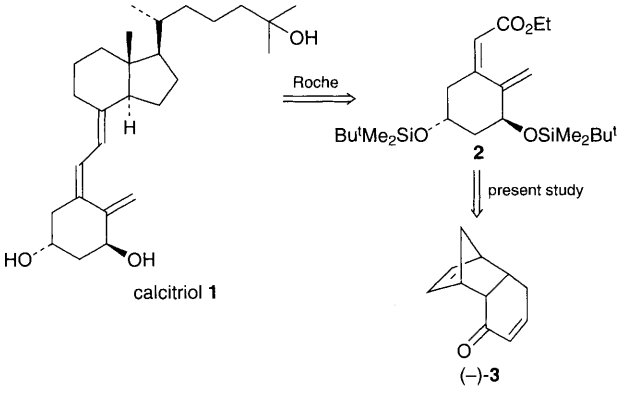
A new and concise enantiocontrolled route to the *A*-ring precursor of calcitriol is developed by utilizing the chiral cyclohexane-2,5-dienone synthon.

Recently, we disclosed[1] an efficient synthesis of the enantiomerically pure tricyclic dienone **3** in both enantiomeric forms by employing lipase-mediated asymmetrization of the *meso*-symmetric precursor and the novel palladium-mediated elimination reaction of the chiral monoacylated products.[2] The enantiomerically pure compound **3** thus obtained was found to have a versatile utility for the construction of a variety of chiral compounds as a chiral cyclohexane-2,5-dienone synthon.[3] We now have found a new utility of this chiral synthon **3** which led to a concise and highly efficient construction of the *A*-ring precursor[4–6] **2** of the Roche synthesis of calcitriol **1**, hormonally active in regulating calcium and phosphorus homeostasis in humans[7] as well as promising in clinical chemotherapy of osteoporosis, psoriasis, cancer, *etc.*[6b] We wish to report here a new approach involving a new methodology which allows a formation of the *A*-ring precursor **2** in > 35% overall yield in ten steps starting from the (−)-enantiomer of the cyclohexadienone synthon[1] (−)-**3**.

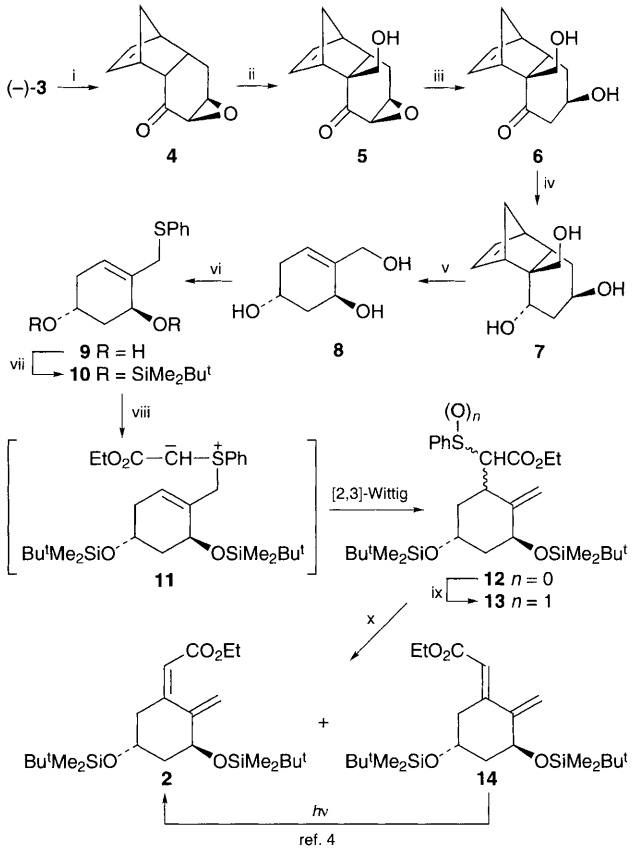
Treatment of (−)-**3** with alkaline hydrogen peroxide afforded stereoselectively the *exo*-epoxide[8] **4**, mp 51–52.5 °C, $[\alpha]_D^{30}$ −9.6 (*c* 1.10, $CHCl_3$), in 90% yield (Scheme 1). A facile hydroxymethylation occurred without affecting the epoxy functionality to give the hydroxy ketone† **5**, mp 137–138 °C, $[\alpha]_D^{30}$ +94.5 (*c* 1.08, $CHCl_3$), in 96% yield as a single product when **4** was exposed to 30% formalin in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene[9] (DBU). Treatment of **5** with the complex,[8,10] generated *in situ* from diphenyl diselenide and sodium borohydride in the presence of acetic acid in ethanol, allowed regioselective epoxy bond cleavage to furnish the keto-diol **6**, mp 123.5–124.5 °C, $[\alpha]_D^{26}$ −141.5 (*c* 1.24, $CHCl_3$), in quantitative yield. This was then reduced from the convex face with sodium borohydride to give stereoselectively the triol **7** which was immediately used for the next reaction.

Upon thermolysis in refluxing diphenyl ether[8] in an open flask in the presence of sodium hydrogen carbonate, the tricyclic triol **7** afforded the cyclohexenetriol **8**, $[\alpha]_D^{28}$ −126.7 (*c* 1.78, EtOH), in 77% yield from **6** with a facile extrusion of cyclopentadiene by retro-Diels–Alder cleavage. Reaction of the triol **8** with diphenyl disulfide in the presence of tributylphosphine in pyridine[11] at room temperature allowed chemoselective substitution at the primary hydroxy centre to give the sulfide-diol **9** which was transformed into the di-*tert*-butyldimethylsilyl ether **10**, $[\alpha]_D^{30}$ +30.9 (*c* 0.87, $CHCl_3$), in 89% yield from **8**.

Having introduced the sulfide functionality at the requisite site, the sulfide **10** obtained was next treated with ethyl diazoacetate in toluene in the presence of a catalytic amount of rhodium(II) acetate[12] or copper(II) hexafluoroacetylacetonate[13] to initiate concurrent ylide formation and the 2,3-Wittig rearrangement. The expected transformation did take place at 80 °C for the rhodium salt and 50 °C for the copper salt to give rise to the *endo*-olefin **12** in comparable yields as a mixture of diasteromers *via* the ylide **11**. Without separation the mixture was oxidized to the sulfoxide[14] **13** which was immediately subjected to the thermolytic elimination reaction in refluxing toluene in the presence of calcium carbonate[15] to give a separable *ca.* 2:3 mixture of the *A*-ring precursor‡ **2**, $[\alpha]_D^{30}$ −49.0 (*c* 0.58, EtOH) (lit. $[\alpha]_D^{25}$ −36.9 (*c* 0.3, EtOH);[4b] $[\alpha]_D^{25}$ −39.5 (*c* 0.88, EtOH)[14])§ and its geometrical isomer **14**, $[\alpha]_D^{28}$ −4.66 (*c* 1.09, EtOH) {lit. $[\alpha]_D^{27}$ −5.2 (*c* 0.56, EtOH);[6c] $[\alpha]_D^{23}$ −4.9 (*c* 0.5, EtOH);[6a] $[\alpha]_D^{25}$ −4.7 (*c* 0.5, EtOH)},¶ in 59% total overall yield from **10** with some recovery of the starting



Scheme 1



Scheme 2 *Reagents and conditions*: i, 30% H_2O_2, 10% NaOH, MeOH, 0 °C (90%); ii, 35% HCHO, DBU, THF, 0 °C (96%); iii, PhSeSePh, $NaBH_4$, AcOH (cat.), EtOH (100%); iv, $NaBH_4$, MeOH; v, PhOPh, $NaHCO_3$, reflux (77% from **6**); vi, PhSSPh, Bu^n_3P, pyridine; vii, $SiMe_2Bu^t$, imidazole, DMF (89% from **8**); viii, N_2CHCO_2Et, $Rh_2(OAc)_4$ (5 mol%), toluene, 80 °C or $Cu(F_3CCOCHCOCF_3)_2$ (10 mol%), 50 °C; ix, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, −78 to −20 °C; x, $CaCO_3$, toluene, reflux (59% from **10**)

material (72% based on the consumed **10**), the latter of which has been reported to be readily isomerized into the former in an excellent yield.[4]

In conclusion, we have expanded the utility of the chiral cyclohexane-2,5-dienone synthon to the vitamin D_3 area by exemplifying a new and concise synthesis of the *A*-ring precursor of calcitriol.

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Footnotes

† Satisfactory analytical (combustion and/or high-resolution MS) and spectral data (IR, ^{1}H NMR, and MS) data were obtained for all new compounds.

‡ Some (*ca.* 20%) of the mixture of **2** and **14** was formed during the 2,3-Wittig rearrangement state.

§ Spectral data were identical with those reported.[4b]

¶ Identical with an authentic material obtained by the different procedure.[6c]

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