Synthesis of a 1α,25-Dihydroxyvitamin D_3 *A* Ring Model by an Acyl Radical Cyclization

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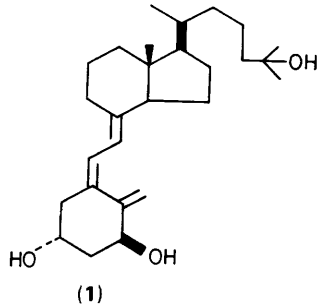
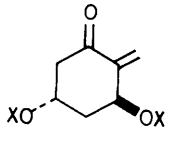
The synthesis of (±)-(**2**), an *A* ring model for 1α,25-dihydroxyvitamin D_3 has been achieved in 7 steps from ethyl acetoacetate, with an acyl radical cyclization as the key ring forming step.

There has been much interest[1] in recent years in the adaptation of radical cyclizations[2] for use in organic synthesis. The vast majority of the methods developed employ the hex-5-enyl to cyclopentylmethyl radical rearrangement as an efficient means of construction of 5-membered rings. However, only a relatively restricted number of examples[1,3] of 6-membered ring construction by radical cyclization have been published. With a view to the eventual synthesis of 1α,25-dihydroxyvitamin D_3 (**1**),[4] the hormonally active form of vitamin D_3, we have undertaken a study of the synthesis of the complex cyclohexanone (**2**) by a radical cyclization process. We report here the successful outcome of these studies.



(**1**)



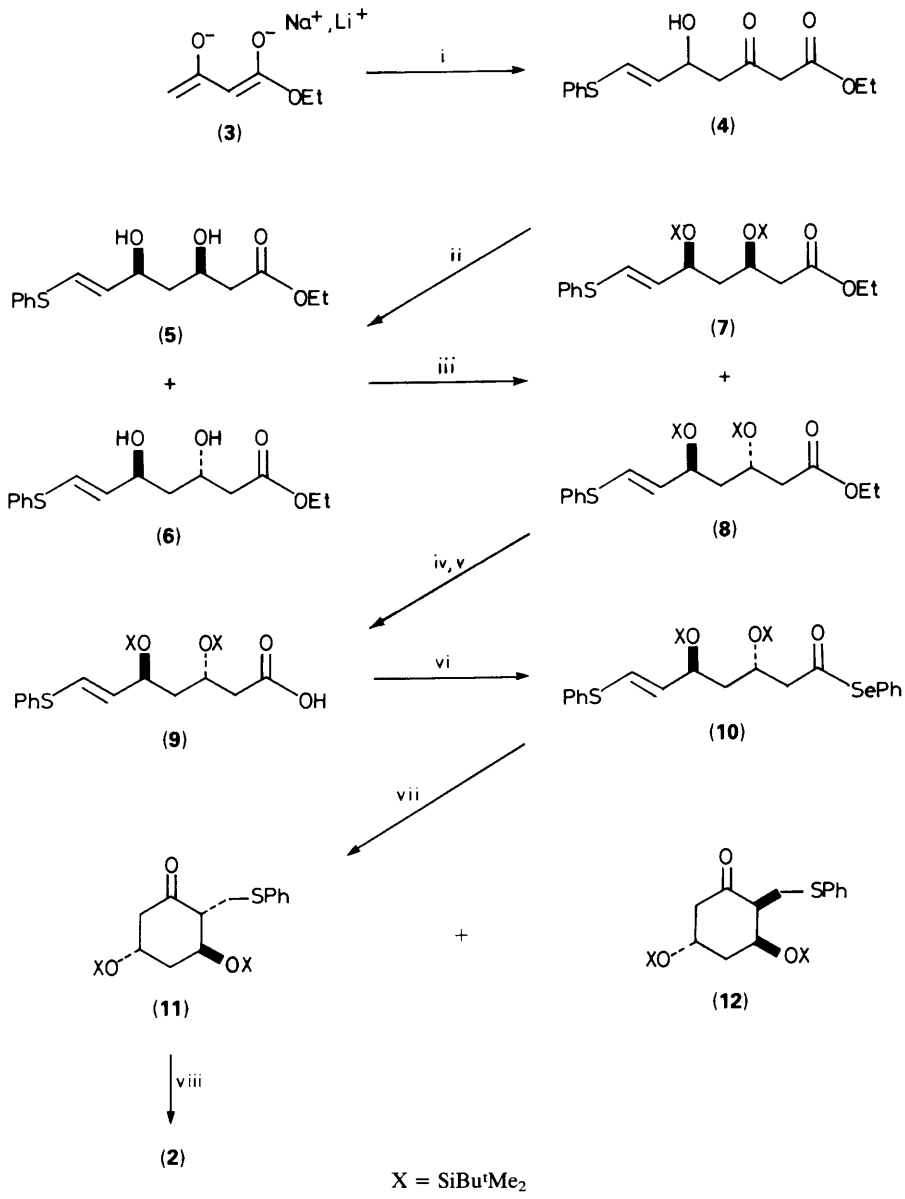
(**2**)

X = $SiBu^tMe_2$

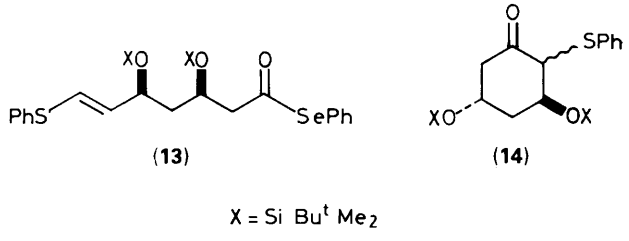
Encouraged by reports[5] in the literature of the formation of cyclohexanones by hept-6-enoyl radical cyclizations, we initially examined[6,7] the effect of substituents on the cyclization of hept-6-ynoyl and hept-6-enoyl radicals generated by the azoisobutyronitrile (AIBN) initiated reaction[8] of acyl selenides with tri-n-butylstannane. We now report that both *syn*- and *anti*-3,5-bis(t-butyldimethylsilyloxy)-7-phenylthiohept-6-enoyl radicals cyclize in excellent yield giving, after chain transfer, highly functionalized cyclohexanones.

Treatment of the Weiler dianion (**3**)[9] with β-phenylthioacrolein, prepared in 47% yield from β-phenylthiopropanal by chlorination with *N*-chlorosuccinimide and subsequent dehydrochlorination, followed by aqueous work-up gave the aldol (**4**)† in 70% isolated yield (Scheme 1). Reduction with tetramethylammonium triacetoxyborohydride in acetic acid/

† All compounds prepared are racemic and gave satisfactory spectroscopic and microanalytical or high resolution mass data.



Scheme 1. *Reagents and conditions*: i, (*E*)-PhSCH=CHCHO, 0 °C, 70%; ii, $Me_4N^+B(OAc)_3H^-$, AcOH, MeCN, −30 °C, 83%, 4.5:1; iii, Bu^{t}Me$_2$SiCl, imidazole, DMF, 86%; iv, separate; v, KOH, MeOH, H_2O, 86%; vi, Et_3N, PhSeCl, Bu_3P, CH_2Cl_2, room temp., 73%; vii, Bu_3SnH, AIBN, C_6H_6, 80 °C, 91%, 1:1; viii, MMPP, H_2O, EtOH then reflux, 60%.



acetonitrile at −30 °C according to Evans[10] gave an 83% yield of a 1:4.5 mixture of *syn*- and *anti*- diols, (**5**) and (**6**). Silylation with t-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF) gave 86% of the corresponding silyl ethers, (**7**) and (**8**), which were separated by chromatography on silica gel. The silylated *anti*-diol (**8**) was saponified and converted to the selenol ester (**10**) by reaction of its triethylammonium salt with phenylselenenyl chloride and tributylphosphine[11] in tetrahydrofuran. The key cyclization was realised by dropwise addition of tri-n-butylstannane and a catalytic quantity of AIBN to a solution of (**10**) in benzene at reflux. Flash chromatography of the crude reaction mixture provided a 1:1 mixture of the cyclohexanones (**11**) and (**12**) in greater than 90% yield. Oxidation of (**11**) with magnesium monoperoxyphthalate (MMPP)[12] gave the corresponding sulphoxides which, as anticipated,[13] gave the target α-methylenecyclohexanone, (±)-(**2**), a white crystalline solid, in 60% yield on heating to reflux in benzene.

The *syn*-bis-silyl ether (**7**) was also converted to the corresponding selenol ester (**13**), which gave the cyclohexanones (**14**) in 81% yield on cyclization in benzene at reflux.

Evidently the 7-phenylthio group has a strong directing effect on the cyclization regiochemistry of heptenoyl radicals, as we had previously observed[6] that closely related selenol esters lacking this group gave significant amounts of cycloheptanones.

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