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ACYL RADICAL CYCLIZATIONS IN SYNTHESIS. PART 1. SUBSTITUENT EFFECTS ON THE MODE AND EFFICIENCY OF CYCLIZATION OF 6-HEPTENOYL RADICALS

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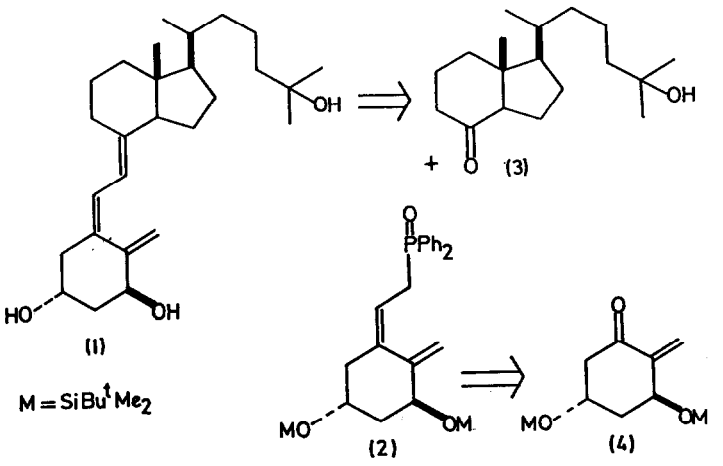
Abstract: The separate, and combined, influences of ether, silyl ether and cyclic ketal groups at positions 3 and 5 on the mode and efficiency of 6-heptenoyl radical cyclizations have been studied with a view to the eventual synthesis of 1α,25-dihydroxyvitamin D_3.

With a view to the eventual synthesis of the important vitamin D_3 metabolite 1α,25-dihydroxyvitamin D_3 (1)[1] we have undertaken a detailed study of the cyclization of acyl radicals onto alkynes[2] and alkenes[3] and into the effect of oxygen based substituents on the efficiency and mode, exo or endo, of such processes. In this paper we report in full the results of our exploratory work in this area.

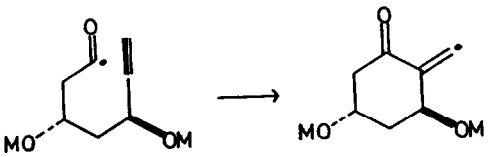
Our initial retrosynthetic analysis of (1) (Scheme 1) reflected that established[4] by Lythgoe and reexamined[5] recently by Baggiolini in which the A ring in the form of phosphine oxide (2) is coupled to the hydroxylated Grundmann/Windaus ketone (3)[5,6] in a Wadsworth-Horner-Emmons reaction. Further disconnection led to the enone (4) as primary target molecule which it was hoped could be elaborated to (2) by Wittig or corresponding chemistry. Alternatively coupling of (3) and (4) could conceivably be achieved by means of acetylide chemistry and subsequent reductive elimination with low valent titanium as employed[7] by Solladié in a recent synthesis of dihydrovitamin D_3.[8,9] Further examination led to the hypothesis that ketone (4) might readily be prepared by cyclization of an acyl radical onto an alkyne as indicated in scheme 2. Moreover it was considered that the acid (5), a precursor of any appropriate acyl radical source would be available in a minimum of steps from 3-hydroxyglutaric acid *via* the known[10] anhydride (6) and chemical[10,11] or enzymic[12] resolution.

When this investigation was begun, and despite the popularity of radicals in organic synthesis, there existed only isolated examples of acyl radical cyclizations onto alkenes[14] and of alkoxycarbonyl radicals onto alkenes[15] and alkynes[16]. However several studies contemporary with the work described here have now been published[17].

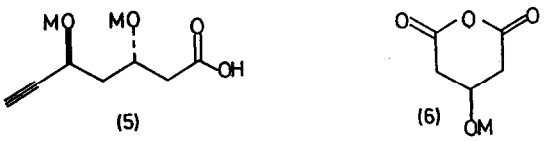
With these aims and background in mind we began our investigation by preparation of a model alkynoic acid (9) by reaction of bis(trimethylsilyl)acetylene with the acid chloride derived from the monomethyl ester of glutaric acid in the presence of tin IV chloride at -78 °C in dichloromethane, essentially according to Nicolaou[18], giving ester (7) in 75% yield. Ketalisation proceeded smoothly to give (8) in 97% yield and saponification with concomitant protodesilylation[19] furnished (9) in 78% yield. An alternative shorter approach, based on the known[20] aluminium trichloride promoted reaction of phthalic anhydride with bis(trimethylsilyl)butadiyne, involving heating glutaric anhydride with bis(trimethylsilyl)acetylene and tin IV chloride in dichloromethane was sluggish and provided only minor quantities of a dihydropyranone (15).



Scheme 1

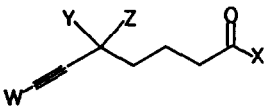


Scheme 2

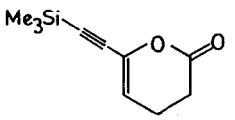


Earlier studies[14] of acyl radical cyclizations had made use of acyl radicals generated by pyrolysis of the appropriate aldehydes with di-*t*-butylperoxide or by the reaction of acyl chlorides with tri-*n*-butylstannane. However bearing in mind the elevated temperatures and prolonged reaction times required in the first instance and the uncertainty[21] concerning the mechanism in the latter, we chose to attempt the reaction thioesters with tri-*n*-butylstannane and a radical initiator. Thus reaction of **(9)** with diphenyl disulphide and triphenylphosphine in toluene at reflux gave a 36% yield of the required thioester **(10)** after prolonged heating. A more efficient procedure involved treatment of **(9)** with diphenyl disulphide and tributylphosphine in toluene at room temperature resulting in the isolation of **(10)** in 97% yield after only 10 mins reaction. An alternative shorter preparation of **(10)** involving reaction of bis(trimethylsilyl)acetylene and tin IV chloride with the acid chloride

derived from the monophenylthio ester of glutaric acid in dichloromethane at 0 °C giving the ketone (**11**) was abandoned owing to contamination of the product with significant quantities of the bisthioester (**16**) from which it could only be separated by careful chromatography. Attempted reaction of (**10**) with tri-*n*-butylstannane and azoisobutyronitrile (AIBN) with prolonged heating in benzene at reflux and with repeated addition of AIBN gave only recovered starting material and the product of hydrostannylation of the triple bond. Clearly thioesters are not suitable acyl radical precursors, a result since confirmed[17] by Boger and perhaps not too surprising in the light of the low reactivity of thioethers towards stannyl radicals recorded[22] by Beckwith. Evidently the efficient generation of radicals from thioether precursors requires significant stabilisation of the radical as with the acylamino radicals employed[23] by Hart.



(7) X=OMe, Y=Z=O, W=$SiMe_3$
(8) X=OMe, Y—Z=OCH_2CH_2O, W=$SiMe_3$
(9) X=OH, Y—Z=OCH_2CH_2O, W=H
(10) X=SPh, Y—Z=OCH_2CH_2O, W=H
(11) X=SPh, Y—Z=O, W=H
(12) X=SePh, Y—Z=OCH_2CH_2O, W=H
(13) X=OH, Y—Z=OCH_2CH_2O, W=$SiMe_3$
(14) X=SePh, Y—Z=OCH_2CH_2O, W=$SiMe_3$



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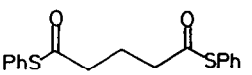

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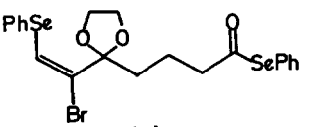
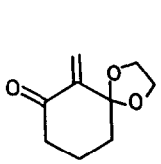


(17)

Attention was then turned to selenol esters, a class of compounds which it had previously been demonstrated[24] react efficiently with stannyl radicals to form acyl radicals. Thus reaction of acid (**9**) with phenylselenyl bromide and tributylphosphine in tetrahydrofuran at room temperature led smoothly to the selenol ester (**12**), a pale yellow oil, together with the vinyl selenide (**17**) in 54 and 33% yields respectively. In our hands the combination of phenylselenyl bromide, or chloride, with tributylphosphine is equally as effective as the combinations of the less readily available and/or more expensive phenylselenocyanate and *N*-phenylselenylphthalimide with tributylphosphine advocated[25] by Grieco and Nicolaou for the preparation of selenol esters from acids. The regiochemistry of addition of phenylselenyl bromide across the acetylenic bond leading to (**17**) was assigned on the basis of the chemical shifts of the vinylic proton and carbon nuclei (^1H δ: 5.50 and ^{13}C δ: 143 and 110.5) by comparison with the work[26] of Garrett in related systems. In contrast

to the work[27] of Toru on 4-pentynoic acids and phenylselenyl chloride no selenolactonisation was observed leading to the conclusion that (17) is the product of further reaction of (12) with the reagents and that the combination of phenylselenyl bromide with tributylphosphine is more reactive towards carboxylic acids than carbon-carbon multiple bonds. Alternatively (12) was prepared in 71% yield by treatment of its derived acyl chloride with sodium phenylseleno(triethoxyborate)[28] prepared *in situ* by reaction of diphenyl diselenide with sodium borohydride.[29]

Reaction of (12) with tri-*n*-butylstannane and AIBN in benzene at reflux led to a complex mixture of products which did not contain either of the expected products (18) and (19). Careful chromatography of the crude reaction mixture provided the major component (20) in 22% yield and a minor amount of a second compound tentatively identified as (21). Clearly hydrostannylation of the triple bond and quenching of the acyl radical by hydrogen abstraction from the stannane were competing effectively with the required cyclization. The product (21) is thought to arise by reduction of the selenol ester to the aldehyde which then serves to trap a vinyl radical produced on addition of a stannyl radical to the acetylene. The efficient formation of cyclohexanols by radical cyclization onto aldehydes has been recently demonstrated[30] by Fraser-Reid and verified[31] by Beckwith.



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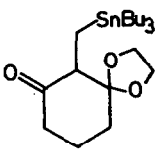

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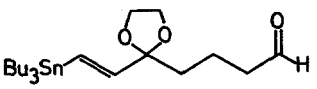

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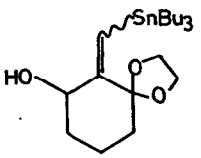
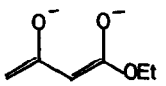


(21)

In order to avoid hydrostannylation of the triple bond we sought to prepare the temporarily hindered selenol ester (14). Thus treatment of a preformed mixture of acid (9) and excess chlorotrimethylsilane in THF at -78 °C with two equivalents by lithium hexamethyldisilazide followed by aqueous work-up gave the acid (13) which on treatment with phenylselenyl bromide and tributylphosphine cleanly yielded the required ester (14). The generation of the acetylide anion in the presence of chlorotrimethylsilane generally proved more efficient than sequential addition of base and the chlorosilane. Treatment of selenol ester (14) with tributylstannane under the standard conditions again led to a complex mixture of products from which no cycloalkanones were isolated. The possibility that the ethylene ketal in the acyl radicals derived from (12) and (14) was preventing cyclization was ruled out when selenol ester (25), prepared from the Weiler dianion (22)[32] by a sequence of reactions involving alkylation to (23), ketalisation to (24), saponification and selenol esterification, also led to a complex reaction mixture on reaction with tributylstannane under the standard conditions.

Clearly the cyclization of 6-heptynoyl radicals is extremely inefficient, possibly owing to unfavourable steric interactions in the transition state.[2] We were therefore compelled to turn our attention to the cyclization of 6-

heptenoyl radicals. As indicated above prior to our work there was a limited amount of literature precedent for the formation of cyclohexanones by a 6-*exo*-trig process with acyl radicals.[14] Subsequently an example of a vinyl radical initiated 6-*exo*-trig reaction has been published.[33]



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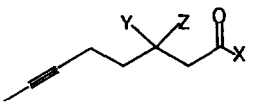


(23) X=OEt, Y=Z=O

(24) X=OEt, Y—Z=OCH_2CH_2O

(25) X=SePh, Y—Z=OCH_2CH_2O

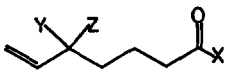
Hydrogenation of acid (9) over Lindlaar's catalyst gave the corresponding alkene (26) which was converted to the selenol ester (27) by reaction with *N*-phenylselenophthhalimide and tributylphosphine. Reaction of (27) with tri-*n*-butylstannane and AIBN under the standard led conditions cleanly to the reduction product (28) and the cycloheptanone (36) in 55 and 32% yields respectively. No evidence was obtained for formation of the anticipated cyclohexanone.

A further model selenol ester (31) was prepared by alkylation of diethyl malonate with 3-chloropropanal diethyl acetal giving (33) which, after titanium IV chloride mediated condensation with bis(trimethylsilyl)acetylene according[34] to Johnson giving (34) and decarboxyethylation[35] with concomitant protodesilylation, gave the acetylenic ester (35). Hydrogenation over Lindlaar's catalyst provided the allylic ether (29), which after saponification to (30), was converted to (31) by treatment of the derived acyl chloride with sodium borohydride/diphenyl diselenide. Reaction of (31) with tri-*n*-butylstannane and AIBN under the usual conditions gave aldehyde (32) and cycloheptanone (37) in 35 and 27% yields respectively. A trace quantity of cyclohexanones (38) was also isolated from the experiment.

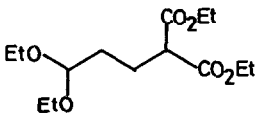
With a view to examining the effect of oxygen functionality in the 3-position of 6-heptenoyl radicals the selenol esters (39) and (40) were prepared from ethyl 3-ketohept-6-enoate[32] by ketalisation, saponification and selenol esterification or borohydride reduction, silylation, saponification and selenol ester formation respectively. Reaction of (39) with tri-*n*-butylstannane and AIBN in benzene at reflux gave 10% of aldehyde (41) and 84% of an inseparable 6:1 mixture of cyclohexanone (43) and cycloheptanone (44). Similar treatment of (40) provided aldehyde (42) in 9% yield, a mixture (1:1) of cyclohexanones (45) and (46) in 41% yield and cycloheptanone (47) in 11% yield.

Examination of the table clearly indicates that not only do 5-oxygenated-hept-6-enoyl radicals not cyclize efficiently but also that they give the product of 7-*endo*-trig mode cyclization (entries 1 and 2) whilst 3-oxygenated hept-6-enoyl radicals cyclize much more efficiently and largely in the 6-*exo*-trig mode (entries 3 and 4). The largely efficient cyclization observed with (39) and (40) is readily understood in terms of the 'Thorpe-Ingold' effect. However the poor cyclization yields and preferential cycloheptanone formation from (27) and (31) are less readily explained and could result from a number of factors including preferred conformations[36] of the allylic ether moieties favouring direct *endo*-cyclization or alternatively initial *exo*-mode

cyclization followed by ring expansion either *via* cyclopropyloxy radicals[37], or by reversibility of the ring closure step,[38] leading eventually to the cycloheptanon-3-yl radicals stabilised by β-oxygen.[39]



(26) X=OH, Y—Z=OCH_2CH_2O
(27) X=SePh, Y—Z=OCH_2CH_2O
(28) X=H, Y—Z=OCH_2CH_2O
(29) X=OEt, Y=OEt, Z=H
(30) X=OH, Y=OEt, Z=H
(31) X=SePh, Y=OEt, Z=H
(32) X=H, Y=OEt, Z=H



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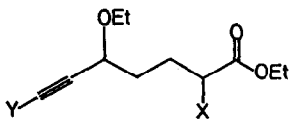
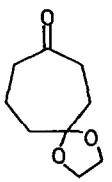


(34) X=CO_2Et, Y=$SiMe_3$
(35) X=Y=H



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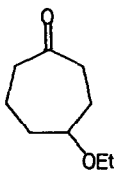

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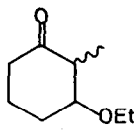

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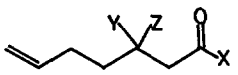
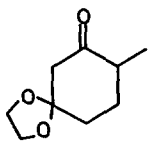


(39) X=SePh, Y—Z=OCH_2CH_2O
(40) X=SePh, Y=$OSiBu^tPh_2$, Z=H
(41) X=H, Y—Z=OCH_2CH_2O
(42) X=H, Y=$OSiBu^tPh_2$, Z=H



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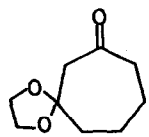

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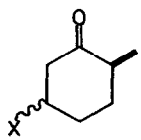
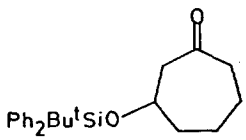
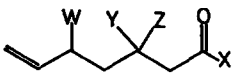


(45) X=α-$OSiBu^tPh_2$
(46) X=β-$OSiBu^tPh_2$



(47)

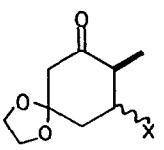
Finally in order to assess the combined effect of ether functions at both the 3- and 5- positions of the hept-6-enoyl radical we prepared the selenol ester (**50**). Thus condensation of the mixed sodium lithium salt of the ethyl acetoacetate dianion (**22**) with acrolein gave the aldol product (**48**)[40] which after silylation and ketalisation gave (**49**). Saponification and selenol ester formation by treatment of the acyl chloride with sodium phenylselenide gave (**50**). Treatment of (**50**) with tri-*n*-butylstannane and AIBN in benzene at reflux led smoothly to a 3:1 mixture of the diastereoisomeric cyclohexanones (**51**) and (**52**) and the cycloheptanone (**53**) in 72 and 24% isolated yields respectively (Table, entry 5). Hence not only does the individual effect of substitution at the 3-position overcome that of substitution at the 5-position, but the combination of the two has a synergic action, probably due to a Thorpe Ingold effect, which greatly improves the overall yield of cyclization.



(48) X=OEt, Y=Z=O, W=OH

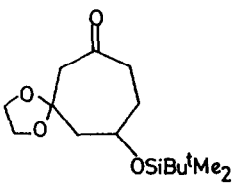
(49) X=OEt, Y—Z= OCH_2CH_2O, W=$OSiBu^tMe_2$

(50) X=SePh, Y—Z=OCH_2CH_2O, W=$OSiBu^tMe_2$



(51) X=β-$OSiBu^tMe_2$

(52) X=α-$OSiBu^tMe_2$



(53)

Table: Cyclization of 6-Heptenoyl Radicals

Entry	Substrate	Products (% Yield)
1	(**27**)	(**29**) (55), (**36**) (32)
2	(**31**)	(**32**) (35), (**37**) (27), (**38**) (1)
3	(**39**)	(**47**) (10), (**43**) + (**44**) (84, 6:1)
4	(**40**)	(**42**) (9), (**45**) + (**46**) (41, 1:1), (**47**) (11)
5	(**50**)	(**51**) + (**52**) (72, 2:1), (**53**) (24)

Further studies on the extension of this work to the synthesis of (**4**) will be reported in due course.

Acknowledgements: We thank the SERC for a studentship (SMF) and the Nuffield Foundation for an equipment grant.

Experimental

Melting points were determined on a Kofler hot stage microscope and are uncorrected. ^{1}H-Nmr spectra were recorded for deuteriochloroform solutions at 60, 200 or 400 MHz with either Jeol PMX 60, Varian XL200 or Varian VXR400 instruments. ^{13}C-Nmr spectra were recorded at 50 or 100 MHz with the Varian XL200 or VXR400 instruments. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard. Mass spectra were recorded at 70eV on a VG 7070H mass spectrometer. All solvents were purified and dried by standard techniques. Tetrahydrofuran was freshly distilled under nitrogen from sodium benzophenone ketyl. Petrol refers to the fraction distilling at 40-60 °C or 60-80 °C. Ether refers to diethyl ether. Tri-*n*-butylstannane was prepared by the action of polymethylhydrogensiloxane on bis(tributyltin) oxide.[41]

5,5-Ethylenedioxyhept-6-ynoic Acid (9). Methyl 5-oxo-7-trimethylsilylhept-6-ynoate (7) (8.0 g, 35.5 mmol), prepared according to Nicolaou[18], was heated to reflux in benzene (25 ml) with ethylene glycol (4.5 g, 72.5 mmol) and a catalytic quantity of *p*-toluenesulphonic acid in a Dean-Stark apparatus with efficient stirring for 5 hrs. After cooling to room temperature the benzene was removed *in vacuo* and the crude reaction mixture taken up in ether (150 ml), washed with water (2 x 50 ml) and dried over magnesium sulphate. Concentration led to the *ketal* (8) as a slight yellow oil (9.3 g, 97%) with δ (60 MHz): 4.0 (4H, m), 3.56 (3H, s), 2.10 (6H, m), 0.20 (9H, s); $\bar{\nu}_{max}$ (film): 2160, 1735 cm^{-1}.

After Kugelrohr distillation (124 °C oven/ 0.4 mmHg) ketal (8) (3.0 g, 11 mmol) was saponified by stirring with potassium hydroxide (1.50 g, 26 mmol) in methanol (15 ml) and water (3 ml) at room temperature for 12 hr. After dilution with water (75 ml) and ether (50 ml) the reaction mixture was acidified with 2M hydrochloric acid and the aqueous phase further extracted with ether (50 ml). The combined organic layers were washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give a white solid which was crystallised from ether-petrol to give the *title acid* (9) as colourless crystals (1.5 g, 75%) with mp 62 °C; δ (60 MHz): 9.70 (1H, bs), 4.02 (4H, d), 2.50 (1H, s), 2.20 (6H, m); $\bar{\nu}_{max}$: 3299, 2110, 1708 cm^{-1}; m/z: 185 (MH$^+$), 167, 159, 97. (Found: C, 58.49; H, 6.42 calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.60%).

S-Phenyl 5,5-Ethylenedioxythiohept-6-ynoate (10). To a stirred solution of the acid (9) (1.20 g, 6.5 mmol) and diphenyl disulphide (2.14 g, 9.8 mmol) in dry toluene (30 ml) at room temperature under a nitrogen atmosphere was added tributylphosphine (2.43 ml, 9.8 mmol) dropwise *via* a syringe. After 10 mins. the reaction mixture was diluted with toluene (75 ml) and washed with 5% sodium hydrogen carbonate (50 ml). After drying over magnesium sulphate and concentration chromatography on silica gel (eluant: petrol-ether 1:1) gave the *thiol ester* (10) as a colourless oil (1.8 g, 97%) with δ (60 MHz): 7.35 (5H, s), 4.00 (4H, m), 2.70 (1H, s), 2.50 (6H, m); $\bar{\nu}_{max}$ (film): 3279, 2110 cm^{-1}; m/z: 276 (M$^+$), 220, 205, 167, 99, 55. (Found: C, 64.53; H, 5.61 calc. for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84%).

Se-Phenyl 5,5-Ethylenedioxyselenohept-6-ynoate (12) and Se-Phenyl 6-Bromo-5,5-ethylenedioxy-7-phenylselenoselenohept-6E-enoate (17) by Reaction of Acid (9) with Phenylselenyl Bromide and Tributylphosphine. To a stirred solution of the acid (9) (0.13 g, 0.7 mmol) and phenylselenyl bromide (0.16 g, 0.7 mmol) in dry dichloromethane (5 ml) at room temperature under an atmosphere of nitrogen was added tributylphosphine (0.17 ml, 0.7 mmol) dropwise *via* a syringe. After completion (tlc) the volatiles were removed *in vacuo* and the reaction mixture chromatographed on silica gel (eluant: dichloromethane) to give first the *vinyl selenide* (17) as a pale yellow oil which solidified on standing (0.20 g, 33%) with mp 74 °C; δ (60 MHz): 7.30 (10H, m), 5.55 (1H, s) 3.95 (4H, s), 2.80 (2H, m), 1.95 (4H, m); δ ^{13}C: 200.09, 140.29, 135.82, 129.31, 110.48, 97.50, 65.18, 47.83, 34.91, 18.96; $\bar{\nu}_{max}$ (film): 3059, 1718, 1575 cm^{-1}; m/z: 481 (M-Br$^+$), 403 (M-PhSe$^+$), 167, 157, 99, 77, 55. (Found: C, 45.87; H, 3.83 calc. for $C_{21}H_{21}BrO_3Se_2$: C, 45.10; H, 3.79%).

Further elution with dichloromethane gave *selenol ester* (12) also as a yellow oil (0.19 g, 54%) with δ (60 MHz); 7.48 (3H, m), 7.38 (2H, m), 3.95 (4H, m), 2.79 (2H, m), 2.51 (1H, s), 1.95 (4H, m); $\bar{\nu}_{max}$ (film): 3279, 2104, 1718 cm^{-1}; m/z: 325 (MH$^+$), 247, 219, 200, 167, 99, 53. (Found: C, 55.34, H, 4.97 calc. for $C_{15}H_{16}O_3Se$: C, 55.74; H, 4.99%).

Se-Phenyl 5,5-Ethylenedioxyselenohept-6-enoate (12) by Reaction of Acid (9) with Oxalyl Chloride and Subsequently Sodium Phenylselenide. The acid (9) (0.56 g, 3.0 mmol) was treated in benzene (5 ml) at room temperature with oxalyl chloride (1 ml) and dimethyl formamide (1 drop). When gas evolution had ceased (30 mins) the volatiles were removed *in vacuo* to give the crude acid chloride which was used without further purification. A solution of diphenyl diselenide (0.47 g, 1.5 mmol) in absolute ethanol (10 ml) was treated at 0 °C under nitrogen atmosphere with a suspension of sodium borohydride (0.11 g, 3 mmol) in ethanol (3 ml) giving a clear colourless solution. To this solution the crude acid chloride in tetrahydrofuran (5 ml) was added dropwise. After 30 mins at room temperature the reaction mixture was poured on to water (100 ml) and extracted with ether (2 x 50 ml). The combined organic phases were washed with water (30 mol), dried on magnesium sulphate and reduced *in vacuo* to a yellow oil which after chromatography on silica gel (eluant: dichloromethane) gave the *seleno ester* (12) (0.70 g, 71%) identical to the sample prepared above.

Reaction of (12) with Tri-*n*-butylstannane. 5,5-Ethylenedioxy-7-(tri-*n*-butylstannyl)-hept-6E-enal (20). Tri-*n*-butyltin hydride (0.54 g, 1.86 mmol) and AIBN (20 mg) in benzene (5 ml) were added dropwise over 10 min to a solution of selenol ester (12) (0.60 g, 1.86 mmol) in benzene (15 ml) at reflux under nitrogen. After completion (tlc) the benzene was removed *in vacuo* and the complex reaction mixture chromatographed on silica gel (eluant: petrol-ether 3:1) to give the *title compound* (20) as a colourless oil (187 mg, 22%) with δ (60 MHz): 9.60 (1H, s), 6.50 (1H, d, J = 13.2 Hz), 5.9 (1H, d, J = 13.2 Hz), 3.80 (4H, s), 2.35 (2H, m), 0.8-2.1 (31H, m); $\bar{\nu}_{max}$ (film): 2712, 1722, 1601 cm^{-1}; m/z: 403 (M-Bu$^+$), 359, 315, 201, 177, 137, 121, 99, 71, 55. (Found: C, 54.98; H, 8.57 calc. for $C_{21}H_{40}O_3Sn$: C, 54.92; H, 8.78%).

Further elution gave an oil (30 mg, 4%) with δ (60 MHz): 5.80 (1H, s), 4.30 (1H, m), 3.90 (4H, s), 2.50 (2H, m), 0.8-2.1 (32H, m); δ (^{13}C): 156, 127, 110, 64, 57, 38, 37, 29, 27, 19, 14, 11; $\bar{\nu}_{max}$ (CH_2Cl_2): 3426, 1618 cm^{-1} and tentatively identified as *3,3-ethylenedioxy-2-(tri*-n-*butylstannylmethylene)-cyclohexanol* (21).

Se-Phenyl 5,5-Ethylenedioxy-7-trimethylsilylselenohept-6-ynoate (14) and Reaction with Tributyltin Hydride. To a solution of the acid (9) (0.84 g, 4.6 mmol) in dry tetrahydrofuran (20 ml) at room temperature under nitrogen was added freshly distilled chlorotrimethylsilane (1.5 ml, 11.8 mmol). After cooling to -78 °C lithium bis(trimethylsilyl)amide in tetrahydrofuran (9.2 ml of 1M, 9.2 mmol) was added. After stirring for 1 hr at -78 °C the reaction mixture was allowed to come to room temperature and then poured on to water (100 ml) and ether extracted (2 x 50 ml). The combined organic layers were dried on magnesium sulphate and after removal of the volatiles *in vacuo* chromatography (eluant: petrol-ether 1:1) gave the *acid* (13) as a colourless oil which solidified on standing (0.30 g, 26%): mp 47 °C (petrol-ether); δ(60 MHz): 4.10-4.00 (4H, m), 2.65-2.50 (2H, m), 1.60 (4H, m), 0.10 (9H, s); $\bar{\nu}_{max}$ (CH_2Cl_2); 2251, 1705 cm^{-1}; m/z: 257 (MH^+), 239, 197, 195, 169, 159, 124, 99, 73.

This acid was converted to the *selenol ester* (14) in 62% yield with phenylselenyl bromide and tributylphosphine as described above for (12). It was a near colourless oil eluted from silica gel with petrol-ether 3:1 and had δ (60 MHz): 7.30 (5H, m), 4.00 (4H, d), 2.75 (2H, m), 1.95 (4H, m), 0.20 (9H, m); $\bar{\nu}_{max}$ (film): 2157, 1721 cm^{-1}; m/z: 381 ($M-Me^+$), 314, 282, 259, 239, 169, 99, 73, 55. (Found: C, 54.65; H, 6.06 calc. for $C_{18}H_{24}O_3SeSi$: C, 54.67; H, 6.12%).

Reaction of this selenol ester with tributyltin hydride and AIBN in benzene as described above for (12) gave a complex reaction mixture from which no products were obtained in sufficient quantity and purity for satisfactory identification.

Ethyl 3-Oxooct-6-ynoate (23). To a stirred suspension of sodium hydride (0.83 g, 27.5 mmol) in dry tetrahydrofuran (60 ml) at 0 °C and under a nitrogen atmosphere was added ethyl acetoacetate (3.25 g, 25 mmol) dropwise. After stirring for a further 10 min at 0 °C n-butyllithium (10.5 ml of 1.6 M, 26.3 mmol) was added dropwise giving rise to an orange-yellow solution. Bromobut-2-yne (4.11 g, 31 mmol) was then added and the resultant reaction mixture stirred for 10 min at 0 °C. The reaction was quenched by addition of 2M hydrochloric acid (20 ml) and ether (45 ml). The aqueous layer was separated and further extracted with ether (2 x 50 ml). The combined organic phases were washed with water (2 x 100 ml) and brine (50 ml) and dried over magnesium sulphate. Filtration and concentration provided a yellow liquid which on fractional distillation afforded (23) as a colourless liquid with bp 114 °C/ 2 mmHg, lit[42] bp 77-83 °C/0.1 mmHg; δ (60 MHz): 4.08 (2H, q), 3.38 (2H, s), 2.80-2.00 (4H, m), 1.70 (3H, t), 1.25 (3H, t); $\bar{\nu}_{max}$ (film): 1741, 1718, 1638 cm^{-1}.

Ethyl 3,3-Ethylenedioxyoct-6-ynoate (24). Ketalisation of (23), as described for (9) above, gave, after chromatography on silica gel (eluant: petrol-ether 2:1) the *ketal* (24) as a pale yellow liquid (57%) with δ (60 MHz): 4.10 (2H, q), 3.93 (4H, s), 2.60 (2H, s), 2.33-1.53 (7H, m), 1.23 (3H, t); $\bar{\nu}_{max}$ (film): 1732, 1040 cm^{-1}; m/z: 226.1209 (M^+, calc. for $C_{12}H_{18}O_4$ 226.1205), 219, 205, 181, 160, 159, 140 139, 117, 95, 89, 87, 86. (Found: C, 63.44; H, 7.97 calc. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%).

Se-Phenyl 3,3-Ethylenedioxyselenooct-6-ynoate (25) and Reaction with Tributyltin Hydride. Saponification of (24), as described for (9) above, gave *3,3-ethylenedioxyoct-6-ynoic acid* as a colourless oil (76%) which

solidified on standing with mp 70-71 °C (petrol-ether); δ (60 MHz): 10.2 (1H, bs), 4.00 (4H, s), 2.70 (2H, s), 2.50-1.65 (7H, m); m/z: 199 (MH^+), 181, 153, 139, 131, 95, 89, 87, 67, 53. (Found: C, 60.69, H, 7.16 calc. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%). Treatment of the acyl chloride, derived by reaction with oxalyl chloride and a catalytic quantity of dimethyl formamide, with sodium phenylselenide in ethanol as described for (12) above gave, after chromatography on silica gel (eluant: petrol-ether 4:1) the *selenol ester* (25) as a colourless oil (79%) with δ (60 MHz): 7.40 (5H, m), 4.00 (4H, s), 3.13 (2H, s), 2.53-1.66 (7H, m); $\tilde{\nu}_{max}$ (film): 1711, 1040 cm^{-1}; m/z: 338 (M^+) 314, 271, 269, 245, 243, 231, 220, 205, 157, 140, 139, 95, 86, 77, 53. (Found: C, 56.95; H, 5.32 calc. for $C_{16}H_{18}O_3Se$: C, 56.98; H, 5.38%). Reaction of this selenol ester with tributyltin hydride and AIBN in benzene at reflux under nitrogen gave a complex reaction from which no products were obtained in sufficient quantity or purity to enable satisfactory characterisation.

5,5-Ethylenedioxyhept-6-enoic Acid (26). Hydrogenation of ynoic acid (9) (2.3 g, 12.4 mmol) in ethanol (100 ml) over Lindlaar's catalyst (0.075 g) poisoned with quinoline (1 ml) at atmospheric pressure for 9 hr gave after filtration, concentration and chromatography on silica gel (eluant: petrol-ether 1:1) the *enoic acid* (26) as a colourless oil (1.5 g, 64%) which solidified on standing with mp 35 °C (petrol); δ (60 MHz): 9.90 (1H, bs), 5.45 (3H, m), 3.95 (4H, s), 2.35 (2H, m), 1.80 (4H, m); $\tilde{\nu}_{max}$ (CH_2Cl_2): 2998, 1708, 1404 cm^{-1}; m/z: 159, 99, 55, 45, 27. (Found: C, 58.06; H, 7.66 calc. for $C_9H_{14}O_3$: C, 58.05; H, 7.57%).

Se-Phenyl 5,5-Ethylenedioxyselenohept-6-enoate (27). To a solution of enoic acid (26) (0.08 g, 0.44 mmol) in dry tetrahydrofuran (5 ml) at room temperature and under an atmosphere of nitrogen was added *N*-phenylselenophthalimide (0.13 g, 0.44 mmol) followed by tributylphosphine (0.15 ml, 0.44 mmol). The resulting solution was stirred for 1 hr at room temperature and then poured on to water (40 ml) and ether extracted (2 x 30 ml). After drying over magnesium sulphate and concentration the crude product was chromatographed on silica gel (eluant: petrol-ether 5:3) to give the *title compound* as a near colourless oil (0.06 g, 40%) with δ (200 MHz): 7.20 (5H, m), 6.00 (3H, m), 3.85 (4H, s), 2.70 (2H, m), 1.75 (4H, m); $\tilde{\nu}_{max}$ (film): 3052, 1721, 1578 cm^{-1}; m/z: 327.0522 (MH^+, calc. for $C_{15}H_{18}O_3Se$: 327.0499), 314, 169, 157, 141, 99, 77, 68, 55, 41, 27.

Reaction of Selenol Ester (27) with Tributyltin Hydride. To a stirred solution of (27) (0.125 g, 0.38 mmol) in benzene (3 ml) at reflux under nitrogen was added a solution of tributyltin hydride (0.159 g, 0.38 mmol) and a catalytic quantity of AIBN in benzene (2 ml) dropwise over 10 min. After completion (30 min, tlc) the reaction was allowed to cool to room temperature and the solvents removed *in vacuo*. Column chromatography on silica gel of the crude reaction mixture (eluant: petrol-ether 1:2) gave *3,3-ethylenedioxyhept-6-enal* (28) as a colourless liquid (36 mg, 55%) with δ (60 MHz): 9.75 (1H, t), 6.00-5.00 (3H, m), 3.95 (4H, d), 2.55 (2H, m), 1.80 (4H, m); $\tilde{\nu}_{max}$ (film): 2945, 1718, 1070 cm^{-1}. Further elution gave *4,4-ethylenedioxycycloheptanone* (36) as a colourless oil (0.021 g, 32%) with δ (400 MHz): 4.00 (4H, s), 2.61 (2H, m), 2.53 (2H, m), 1.93 (2H, m), 1.86 (4H, m); δ (^{13}C): 109.88, 64.55, 43.55, 39.21, 37.45, 33.12, 18.94; $\tilde{\nu}_{max}$ (film): 2945, 1695 cm^{-1}; m/z: 170.0936 (M^+, calc. for $C_9H_{14}O_3$: 170.0943), 142, 113, 99, 86, 55, 42.

Ethyl 2-Carboethoxy-5-ethoxy-7-trimethylsilylhept-6-ynoate (34). To a stirred solution of acetal (33)[43] (0.35 g, 1.2 mmol) in dry dichloromethane (25 ml) at -78 °C under a nitrogen atmosphere was added bis(trimethylsilyl)acetylene (1.00 ml, 4.4 mmol) and then titanium tetrachloride (0.20 ml, 1.7 mmol). After 30 min the reaction was quenched by addition of methanol (1 ml). After warming to room temperature the reaction was partitioned between 1M hydrochloric acid (100 ml) and dichloromethane (100 ml). The organic layer was separated and washed with water (50 ml) and dried over calcium chloride. Filtration and removal of the solvent *in vacuo* gave a brown liquid (0.75 g) containing some titanium dioxide. Chromatography, on silica gel, of this mixture (eluant: petrol-ether 5:2) gave the *title compound* as a colourless liquid (0.34 g, 83%) with δ (200 MHz): 4.16 (4H, q), 4.00 (1H, t), 3.75 (1H, m), 3.34 (2H, m), 1.90 (4H, m), 1.20 (9H, m), 0.14 (9H, s); m/z: 327 ($M-Me^+$), 312, 297, 269, 218, 195, 182, 155, 127, 99.55. (Found: C, 59.36; H, 8.58 calc. for $C_{17}H_{30}O_5Si$: C, 59.62; H, 8.83%).

Ethyl 5-Ethoxyhept-6-enoate (29). To a solution of malonate (34) (0.50 g, 1.5 mmol) in dimethyl sulphoxide (5 ml) was added anhydrous lithium chloride (0.15 g, 3.5 mmol) and water (1 ml). The mixture was heated to 150 °C for 15 hr before being cooled to room temperature, poured onto water (50 ml) and ether extracted (2 x 30 ml). The combined organic extracts were washed with water (30 ml) and brine (30 ml) and dried over magnesium sulphate. Filtration, concentration and chromatography on silica gel (eluant: petrol-ether 3:1) gave *ethyl 5-ethoxyhept-6-ynoate* (35) as a colourless oil (0.16 g, 55%) with δ (60 MHz): 4.20-3.00 (5H, m), 2.30 (1H, d), 2.25-1.40 (6H, m), 1.20 (6H, m).

Hydrogenation of (35) over Lindlaar's catalyst in ethanol, as described above for (26) above, filtration and concentration, gave the *title compound* (29) as a colourless oil (93%) with bp 100 °C (oven)/ 0.7 mmHg; δ (200 MHz): 5.68-5.14 (3H, m), 4.12 (2H, q), 3.65-3.25 (3H, m), 2.31 (2H, m), 1.62 (4H, m), 1.21 (6H, m); $\tilde{\nu}_{max}$ (film): 2972, 1735 cm^{-1}; m/z: 200 (M^+), 173, 155, 127, 109, 99, 88, 85, 81, 61, 57, 55, 43. (Found: C, 65.52; H, 9.93 calc. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%).

5-Ethoxyhept-6-enoic Acid (30). Standard saponification of (29) with potassium hydroxide in aqueous methanol followed by acidification and ether extraction gave the *title compound* (30) as a colourless oil (99%) with bp 125 °C (oven)/0.3 mmHg; δ (400 MHz): 7.27 (1H, s), 5.73-5.64 (1H, m), 5.22 (2H, m), 3.67-3.30 (3H, m), 2.39 (2H, m), 1.65 (4H, m), 1.21 (3H, t); $\tilde{\nu}_{max}$ (film): 3000, 1735, 1708, 1638 cm^{-1}; m/z: 172 (M^+), 145, 127, 109, 99, 85, 81, 67, 57, 55, 43, 41, 29. (Found: C, 62.44; H, 9.55 calc. for $C_9H_{16}O_3$: C, 62.77; H, 9.36%).

Se-Phenyl 5-Ethoxyselenohept-6-enoate (31). To a solution of the acid (30) (0.17 g, 1.0 mmol) in benzene (5 ml) was added sodium hydrogen carbonate (0.084 g, 1.00 mmol) and water (0.1 ml). The mixture was heated to 60 °C and when effervescence had ceased a Dean Stark trap was fitted and the water removed by azeotropic distillation. On cooling to room temperature freshly distilled oxalyl chloride (0.1 ml, 1.0 mmol) was added and the mixture stirred vigorously for 1 hr. The solvent was then removed *in vacuo* to give a mixture of the crude acid chloride and sodium chloride. This mixture was then added to a solution of sodium phenylselenide in ethanol, prepared from diphenyl diselenide (155 mg, 0.5 mmol) and sodium borohydride (38 mg, 1 mmol) as described for (12). Ether extraction and chromatography on silica gel (eluant: dichloromethane)

gave the *selenol ester* (**31**) as a pale yellow liquid (0.08 g, 26%) with δ (60 MHz): 7.30 (5H, m), 6.15-4.90 (3H, m), 3.70-3.10 (3H, m), 2.70 (2H, m), 1.60 (4H, m), 1.20 (3H, t); $\bar{\nu}_{max}$ (film): 3065, 1721, 1578 cm^{-1}; m/z: 312, 265, 183, 155, 127, 109, 85, 81, 67, 55.

Reaction of (31) with Tributyltin Hydride. Dropwise addition of tributyltin hydride (75 mg, 0.26 mmol) and AIBN (1 mg) in benzene (1 ml) to a stirred solution of (**31**) (80 mg, 0.26 mmol) in benzene (5 ml) at reflux under a nitrogen atmosphere, followed by heating to reflux for a further 1 hr, concentration and chromatography on silica gel (eluant: petrol-ether 1:2) gave *5-ethoxyhept-6-enal* (**32**) as a colourless oil (14.1 mg, 35%) with δ (200 MHz): 9.77 (1H, s), 5.68 (1H, m), 5.14 (2H, m), 3.52 (2H, m), 3.27 (1H, m), 2.46 (2H, m), 1.59 (4H, m), 1.10 (3H, t); $\bar{\nu}_{max}$ (film): 1721 cm^{-1}; m/z: 156.1161 (M^+, calc. for $C_9H_{16}O_2$: 156.1150), 129, 112, 100, 93, 85, 72, 67, 57, 43.

Further elution gave *3-Ethoxy-2-methylcyclohexanone* (**38**) an oil (0.4 mg, 1%) as a mixture of two diastereoisomers in the ratio of 3:1 with δ (400 MHz): 0.96 (minor) + 1.21 (major) (3H, 2t), 1.09 (minor) + 1.14 (major) (3H, 2d), 1.4-1.7 (2H, m), 1.95-2.55 (5H, m), 3.05-3.75 (3H, m) and finally *4-ethoxycycloheptanone* (**37**) a colourless oil (11 mg, 27%) with δ (200 MHz): 3.50 (3H, m), 2.70 (1H, m), 2.45 (2H, m), 2.30 (1H, m), 2.00-1.80 (5H, m), 1.55 (1H, m), 1.20 (3H, t); δ (^{13}C): 214.60, 77.45, 63.61, 43.60, 37.66, 35.08, 28.91, 18.65, 15.59; $\bar{\nu}_{max}$ (film): 1698 cm^{-1}; m/z: 156.1143 (M^+, calc. for $C_9H_{16}O_2$: 156.1150), 128, 110, 85, 72, 69, 55.

Ethyl 3,3-Ethylenedioxyhept-6-enoate was prepared by ketalisation of ethyl 3-oxohept-6-enoate[32] as described above for (**9**). It was a colourless oil (79%) with δ (200 MHz): 5.86 (1H, m), 5.01 (2H, m), 4.20 (2H, q), 4.02 (4H, s), 2.68 (2H, s), 2.18 (2H, m), 1.94 (2H, m), 1.28 (3H, t); $\bar{\nu}_{max}$ (film): 3075, 1735, 1638 cm^{-1}; m/z: 214.1212 (M^+, calc. for $C_{11}H_{18}O_4$: 214.1205), 159, 127, 117, 89, 83, 55, 43.

3,3-Ethylenedioxyhept-6-enoic Acid an oil, prepared (69%) by standard saponification of ethyl 3,3-ethylenedioxyhept-6-enoate, had bp 150 °C (oven)/0.5 mmHg; δ (200 MHz): 10.0 (1H, bs), 5.82 (1H, m), 4.96 (2H, m), 4.02 (4H, s), 2.71 (2H, s), 2.14 (2H, m), 1.92 (2H, m); $\bar{\nu}_{max}$ (film): 3072, 1708, 1638 cm^{-1}; m/z: 187 (MH^+), 141, 132, 131, 127, 110, 102, 97, 89, 87, 83, 82, 55. (Found: C, 58.51; H, 7.91 calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.57%).

Se-Phenyl 3,3-Ethylenedioxyselenohept-6-enoate (**39**) was prepared from 3,3-ethylenedioxyselenohept-6-enoic acid by treatment of the acid chloride with sodium phenylselenide in ethanol as described for (**12**) above. It was a pale yellow oil (63%), eluted from silica gel with dichloromethane, with δ (200 MHz): 7.48 (2H, m), 7.38 (3H, m), 5.80 (1H, m), 4.95 (2H, m), 4.00 (4H, s), 3.05 (2H, s), 2.16 (2H, m), 1.90 (2H, m); $\bar{\nu}_{max}$ (film): 3072, 1711, 1638 cm^{-1}; m/z: 270.9871 ($M-CH_2{=}CHCH_2CH_2^+$ calc. for $C_{11}H_{11}O_3Se$: 270.9873), 243, 157, 128, 127, 86, 84, 77, 55.

Reaction of Selenol Ester (39) with Tributyltin Hydride

To a stirred solution of (**39**) (0.15 g, 0.46 mmol) in benzene (4 ml) at reflux under nitrogen was added tributyltin hydride (0.20 g, 0.7 mmol) and a catalytic quantity of AIBN in benzene (1 ml) over 10 min. After