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Studies Towards the Synthesis of Obtusenyne. A Claisen Rearrangement Approach to Unsaturated Nine-membered Lactones.

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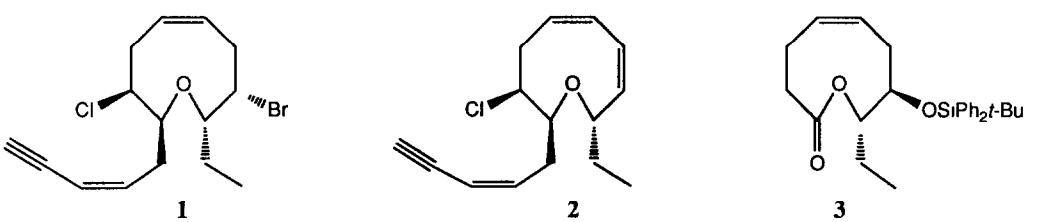
Abstract: *An advanced intermediate for the synthesis of the* Laurencia *oxonane natural product obtusenyne 1, namely the unsaturated nine-membered lactone 3, was efficiently prepared in seven steps from* (E)*-3-hexenoic acid 7 The key transformation was the Claisen rearrangement of the vinyl ketene acetal 4, which represents novel methodology for the preparation of such unsaturated nine-membered lactones*

A host of nonterpenoid C_{15} metabolites have been isolated from red algae of the genus *Laurencia*, as well as the opisthobranchs that feed upon them [1,2,3] Among these are a number of halogenated nine-membered ring cyclic ethers (oxonanes), such as obtusenyne **1**[4,5] and brasilenyne **2**[6] (Figure 1) Our planned strategy[7,8] for the synthesis of these challenging marine natural product targets required the preparation of the 5,6-unsaturated 2-oxonanone **3**



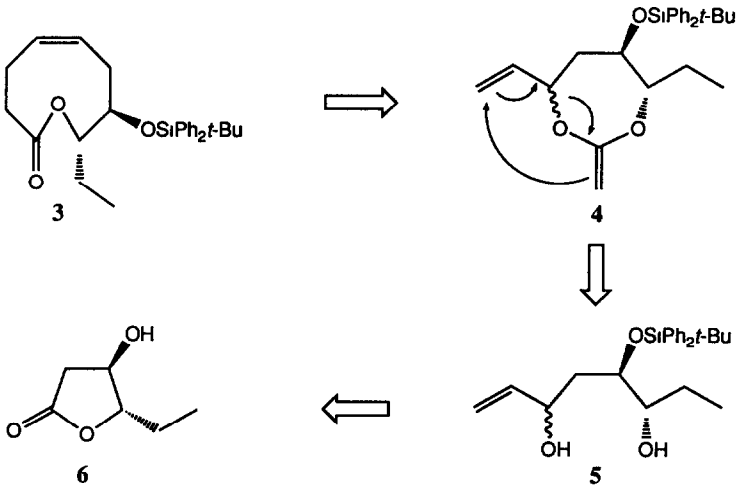
1 **2** **3**

Figure 1

The cyclization of acyclic precursors to form nine-membered lactones is generally an unfavourable process,[9] although incorporation of a (Z)-double bond into the chain of a ω-hydroxy acid can lead to acceptable yields for lactonisation [10,11] Carbon-carbon bond forming cyclization approaches[12,13] and ring expansion reactions [14,15] provide the remaining examples of a rather limited range of methods for the synthesis of unsaturated nine-membered lactones This paper describes development of a Claisen rearrangement strategy for the synthesis of the lactone **3**, based upon the method used previously by us for the preparation of unsaturated eight-membered lactones [16] Petrzilka had previously applied this procedure to the synthesis of the naturally occurring ten-membered lactone phoracantholide J [17]

RESULTS AND DISCUSSION

Synthesis of the unsaturated nine-membered lactone **3** by the planned Claisen rearrangement strategy required preparation of the vinyl ketene acetal **4** (Scheme 1) from the 1,4-diol **5** and a ketene equivalent [16] The preparation of the diol **5** from the known lactone **6**[18] is now described

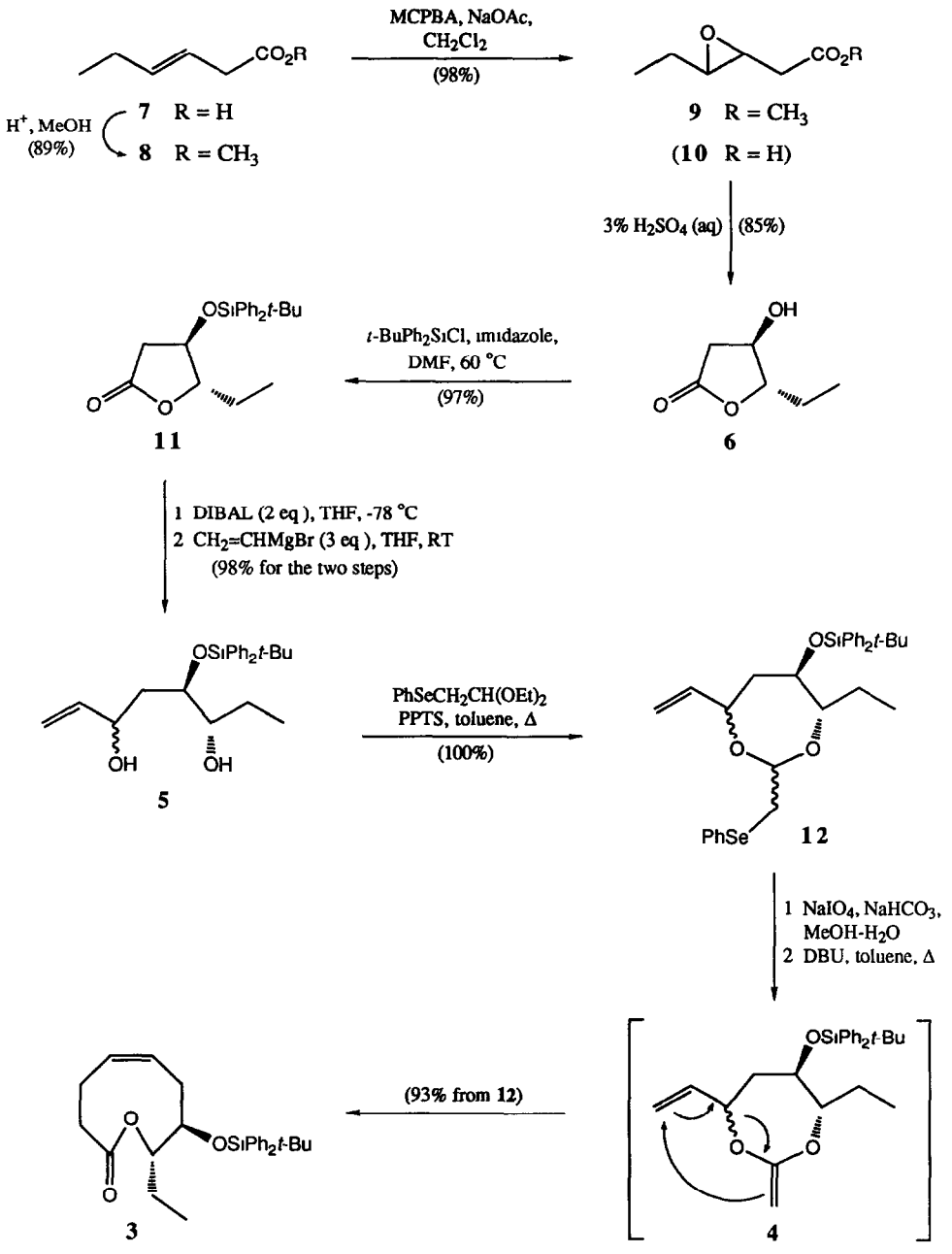


Scheme 1

Acid treatment of 3,4-epoxyhexanoic acid (**10**) was reported by Falbe[18] to give a 2 1 mixture of the hydroxy γ-lactone **6** together with the corresponding β-lactone In our hands attempted epoxidation of **7** with either peracetic acid or *meta*-chloroperbenzoic acid (MCPBA) failed to give the required epoxy-acid **10** However, the same authors reported that acid treatment of the corresponding epoxy esters gave the hydroxy γ-lactones selectively This alternative approach to the hydroxy γ-lactone **6** was utilised

Epoxidation of methyl (*E*)-3-hexenoate **8** with MCPBA gave the epoxy ester **9** in excellent yield (Scheme 2) Treatment of **9** with 3% aqueous sulphuric acid gave the hydroxy γ–lactone **6**, with no evidence of β-lactone formation [18] However, repeated extraction of the aqueous reaction mixture was necessary to achieve a good yield The robust *tert*-butyldiphenylsilyl group[19] was chosen for protection of the hydroxy lactone **6**, since removal was expected to be late in the synthetic sequence to obtusenyne **1** and such protection was known to be stable under the Claisen rearrangement conditions [16] Thus, the hydroxy lactone **6** was converted into the silyloxy compound **11** using *tert*-butyldiphenylchlorosilane and imidazole in anhydrous DMF at 60 °C

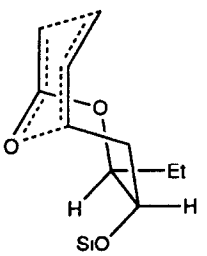
The protected hydroxy lactone **11** was transformed into the 1,4-diol **5** *via* a two step procedure Reduction using two equivalents of diisobutylaluminium hydride (DIBAL), to ensure complete reaction, and quenching at low temperature followed by an extractive work-up gave the corresponding lactol This was treated, without further purification, with an excess of vinylmagnesium bromide to afford the diol **5** (98% yield for the two steps) Attempts to carry out the conversion as a 'one-pot' process resulted in only a moderate overall yield of the diol **5**


MCPBA, NaOAc,
CH2Cl2
(98%)
CO2R
H+, MeOH
(89%)
7 R = H
8 R = CH3
9 R = CH3
(10 R = H)
3% H2SO4 (aq)
(85%)
OSiPh2t-Bu
t-BuPh2SiCl, imidazole,
DMF, 60 °C
(97%)
OH
11
6
1 DIBAL (2 eq), THF, -78 °C
2 CH2=CHMgBr (3 eq), THF, RT
(98% for the two steps)
PhSeCH2CH(OEt)2
PPTS, toluene, Δ
(100%)
PhSe
12
5
1 NaIO4, NaHCO3,
MeOH-H2O
2 DBU, toluene, Δ
(93% from 12)
3
4

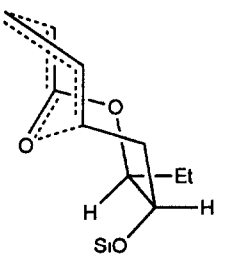
Scheme 2

The diol **5** was treated with phenylselenoacetaldehyde diethylacetal[16,20] in refluxing toluene, under mild acid catalysis, to give the dioxepane **12** in quantitative yield. Pyridinium *p*-toluenesulphonate (PPTS) proved to be a superior catalyst to either Amberlite IR120 gel-type or Amberlyst 15 macroreticular sulphonic acid resins [21] The product was isolated as a mixture of three diastereoisomers, as evident by ^{1}H NMR, which were not separated Oxidation to the corresponding selenoxides was carried out using sodium periodate After extractive work-up and drying, the crude product was heated in refluxing toluene in the presence of 1,8-diazabicyclo[5 4 0]undec-7-ene (DBU) under relatively high dilution conditions (1 mmol/100 ml), conditions which had been optimised in a model study An excellent yield of the unsaturated nine-membered lactone **3** was obtained, *via* Claisen rearrangement of the presumed ketene acetal intermediate **4** The product lactone **3** appeared to be a single isomer by ^{1}H & ^{13}C NMR and TLC The double bond geometry was assumed to be *cis* from an analysis of the likely transition states

Claisen rearrangment of the vinyl ketene acetal **4** could either occur *via* a chair-like (**C**) or a boat-like transition state (**B**) (Figure 2) The former would result in *cis*-double bond geometry for the product lactone **3**, whereas the latter would produce the *trans*-geometry Molecules which can readily adopt either arrangement prefer the chair-like transition state [22,23,24] Also recent work by Paquette provided compelling evidence that a closely related Claisen rearrangement to form a cyclooctenone proceeded *via* a chair-like transition state [25] Thus, transition state **C** would seem to be the more favourable for rearrangement of the vinyl ketene acetal **4**, suggesting the preferred *cis*-double bond geometry for the unsaturated lactone **3**, as shown This was supported by a ^{1}H NMR decoupling experiment which revealed that the coupling constant between the olefinic protons of the lactone **3** was 11 Hz, fully consistent with the assigned *cis*-geometry [26]



C



B

Figure 2

The route employed for synthesis of the unsaturated lactone **3** was highly efficient Nine reactions were carried out, requiring purification by distillation or chromatography at seven of the steps, in an overall 65% yield from inexpensive (*E*)-3-hexenoic acid **7** The key Claisen rearrangement step proceeded in 93% yield Elaboration of the lactone **3** to a nine-membered ring ether, appropriately functionalised for the synthesis of obtusenyne **1**, will be reported in due course [27]

EXPERIMENTAL

NMR spectra were recorded using Bruker WM250 and WM400 instruments IR spectra were determined on a Perkin-Elmer 1310 spectrophotometer, calibrated relative to polystyrene Low and high resolution electron impact (EI) mass spectra were recorded on AEI MS902 and MS30 instruments, respectively Chemical ionisation (CI) mass spectra were recorded by Dr J Ballantine and co-workers at the S E R C Mass Spectrometry Service Centre, Swansea Microanalyses were performed by Mr D Flory and staff at the University Chemical Laboratory, Cambridge M p s were determined on a Buchi 510 apparatus Flash chromatography[28] was carried out on Merck Kieselgel 60 (230-400 mesh) and thin layer chromatography was carried out on Merck Kieselgel 60 GF254 plates, coated to a thickness of 0 25mm. THF refers to tetrahydrofuran distilled from potassium in a recycling still Other dry solvents were purified by standard techniques [29]

Methyl (E)-3-hexenoate **8**

(*E*)-3-Hexenoic acid **7** (7 27 g, 63 7 mmol) was stirred overnight in methanol (75 ml) containing conc sulphuric acid (3 75 ml) The mixture was poured into water (50 ml) and extracted with dichloromethane (3 x 100 ml) The combined extracts were dried, concentrated and the residue purified by distillation to give the title ester **8**[30] as a colourless liquid (7 24 g, 89%), b p 56 °C at 18 mm Hg [lit , 67-68 °C at 34 mm Hg], R_f (1 1 ether/hexane) 0 53, ν_{max} (CCl_4) 1740vs (C=O) cm^{-1}, δ_H (250 MHz, $CDCl_3$) 0 97 (3H, t, *J* 7 Hz, CH_3), 2 04 (2H, m, allylic CH_2), 3 02 (2H, d, *J* 6 Hz, CH_2CO), 3 67 (3H, s, OCH_3), 5 55 (2H, m, CH=CH), δ_C (100 MHz, $CDCl_3$) 13 4 (CH_3), 25 5 (CH_2), 37 9 (CH_2CO), 51 7 (OCH_3), 120 4, 136 4 (CH=CH), 172 7 (C=O), *m/z* (EI) 128 (M^+, 53%), (Found M^+, 128 0833 Calculated for $C_7H_{12}O_2$ *M*, 128 0837)

Methyl 3(R),4(R*)-epoxyhexanoate* **9**

73% MCPBA (22 05 g, 106 mmol) was added portionwise to a mechanically stirred suspension of methyl (*E*)-3-hexenoate **8** (10 22 g, 79 7 mmol) and sodium acetate (20 0 g, 240 mmol) in dichloromethane (800 ml) at 0 °C The mixture was stirred at RT overnight The solid was filtered off and the filtrate was washed with saturated aqueous sodium sulphite (500 ml), saturated aqueous $NaHCO_3$, water, then brine The aqueous phases were washed with dichloromethane (2 x 200 ml) and the combined organic extracts were dried and concentrated Flash chromatography of the residue afforded the title *epoxy ester* **9** (11 22 g, 98%), as a colourless liquid, R_f (1 1 ether/hexane) 0 40, ν_{max} (CCl_4) 1745vs (C=O) cm^{-1}, δ_H (250 MHz, $CDCl_3$) 0 99 (3H, t, *J* 7 Hz, CH_3), 1 59 (2H, m, CH_2), 2 51 (1H, dd, A of ABX, J_{AB} 16 Hz, J_{AX} 6 Hz, CH_2CO), 2 59 (1H, dd, B of ABX, J_{AB} 16 Hz, J_{BX} 6 Hz, CH_2CO), 2 73 (1H, dt, *J* 6, 2 Hz, CH-O), 3 03 (1H, dt, *J* 6, 2 Hz, CH-O), 3 71 (3H, s, OCH_3), δ_C (100 MHz, $CDCl_3$) 9 7 (CH_3), 24 7 (CH_2), 37 5 (CH_2CO), 51.8, 53 6, 59 6 (2 x CH-O and OCH_3), 170 9 (C=O), *m/z* (EI) 144 (M^+, 0 1%), 143 (0 2), 129 (*M*-CH_3, 1), 128 (*M*-16, 0 5), 127 (2), 113 (*M*-OCH_3, 4), 112 (6), 88 (27), 87 (100), (Found C, 58 55, H, 8 6 $C_7H_{12}O_3$ requires C, 58 3, H, 8 4%)

4(R)-Hydroxy-5(S*)-ethyl-4,5-dihydro-2(3H)-furanone* **6**

The epoxy ester **9** (5 71 g, 39 6 mmol) was stirred overnight in 3% aqueous sulphuric acid (50 ml) The product was extracted with dichloromethane (8 x 100 ml), dried and purified by flash chromatography (ether) to give the title hydroxy γ-lactone **6**[18] as a colourless liquid (4 40 g, 85%), R_f (ether) 0 20, ν_{max} (CCl_4) 3620m (O-H), 3450s (O-H), 1790vs (C=O) cm^{-1}, δ_H (250 MHz, $CDCl_3$) 1 03 (3H, t, *J* 7 Hz, CH_3), 1 65 (2H, m, CH_2), 2 36 (1H, br s, OH), 2 52 (1H, dd, *J* 18, 4 Hz, CH_2CO), 2 83 (1H, dd, *J* 18, 6 Hz, CH_2CO), 4 29 (2H, m, 2 x CH-O), δ_C (100 MHz, $CDCl_3$) 9 5 (CH_3), 26 1 (CH_2), 37 7 (CH_2CO), 71 1, 89 3 (2 x CH-O), 175 7 (C=O), *m/z* (EI) 113 (*M*-OH, 3%), 102 (*M*-CO, 19), 83 (12), 59 (100), *m/z* (CI, NH_3) 148 [$(M+NH_4)^+$, 100%], 131 [$(M+H)^+$, 15], (Found· $(M+NH_4)^+$, 148 0974 Calculated for $C_6H_{10}O_3$ $M+NH_4$, 148 0984)

4(R)-tert-Butyldiphenysilyloxy-5(S*)-ethyl-4,5-dihydro-2(3H)-furanone* **11.**

The hydroxy γ-lactone **6** (3 935 g, 30 2 mmol), imidazole (4 53 g, 66 5 mmol) and *tert*-butyldiphenylchlorosilane (8 6 ml, 33 mmol) were stirred at 60 °C in dry DMF (25 ml) overnight. After allowing the solution to cool, it was poured into water (125 ml) and extracted with ether (3 x 100 ml) The extracts were washed with brine (50 ml), combined and dried. The residue after evaporation was purified by flash chromatography (2·1 dichloromethane/hexane as eluant) to yield the title *γ-lactone* **11** as a colourless, viscous oil (10 79 g, 97%) The oil crystallised on storage in the freezer, and was recrystallised from hexane to give a white solid, m p 64-65 °C, R_f (CH_2Cl_2) 0 41, ν_{max} (CCl_4) 1790vs (C=O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0 75 (3H, t, *J* 7 Hz, CH_3), 1 06 (9H, s, $C(CH_3)_3$), 1 31 (2H, m, CH_2), 2 50 (2H, m, CH_2CO), 4 17 (1H, m, CH-O), 4 27 (1H, m, CH-O), 7 42 (6H, m, Ar), 7 62 (4H, m, Ar), δ_C (100 MHz, $CDCl_3$) 9 4 (CH_3), 19 0 ($C(CH_3)_3$), 25 7 (CH_2), 26 8 ($C(CH_3)_3$), 37 8 (CH_2CO), 72 4, 89 3 (2 x CH-O), 128 0, 130 2, 132 78, 132 83, 135 67, 135 71 (Ar), 175 2 (C=O), *m/z* (EI) 311 (*M*-*t*-Bu, 66%), 269 (100), *m/z* (CI, NH_3) 386 [$(M+NH)^+$, 100%], (Found C, 71 4, H, 7 7 $C_{22}H_{28}O_3Si$ requires C, 71 7, H, 7 7%)

5(R)-tert-Butyldiphenylsilyloxy-3(R*,S*),6(S*)-dihydroxy-1-octene* **5**

A solution of the lactone **11** (6 60 g, 17 9 mmol) in dry THF (95 ml) was cooled to -75 °C and DIBAL (1 0 M in hexane, 36 0 ml, 36 0 mmol) was added dropwise The mixture was stirred at -70 °C for an hour, then the excess DIBAL was quenched by dropwise addition of saturated ammonium chloride (6 ml), at such a rate as to maintain the temperature below -60 °C A solution of aqueous 10% HCl (12 ml) was added, the cooling bath removed, and the mixture was stirred for 30 minutes The reaction mixture was poured into 10% aqueous HCl (100 ml) and extracted with ether (3 x 500 ml) The extracts were washed with 10% aqueous HCl (100 ml) and brine (100 ml), combined and dried over sodium sulphate The drying agent was filtered off, the filtrate was concentrated, and the residue was dried under high vacuum to give the crude lactol The material was dissolved in dry THF (120 ml) and cooled to -5 °C. Vinylmagnesium bromide (1 0 M in THF, 54 ml, 54 mmol) was added, while the temperature was maintained below 5 °C The cooling bath was removed and the solution was stirred at RT for three hours The reaction mixture was cautiously poured into 5% aqueous HCl (120 ml), with cooling in an ice bath, and extracted with ether (3 x 600 ml) The ether extracts were washed with brine (120 ml), combined and dried The product was purified by flash chromatography (1 1 ether/hexane) to furnish the title *diol* **5**, as a pale yellow oil and an approximately 1.1 ratio of diastereoisomers (7 01 g, 98% over the two steps), R_f (1 1 ether/hexane) 0 24, ν_{max} (CCl_4) 3600m (O-H), 3440m (O-H) cm-1, δ_H (250 MHz, $CDCl_3$) 0 79 (3H, m, CH_3), 1 08 (9H, s, $C(CH_3)_3$), 1.23-1.74 (4H, m, 2 x CH_2), 2 33 (2H, br, 2 x OH), 3 55 (1H, m, CH-O), 3 8-4.5 (2H, 4 x m, 2 x CH-O), 4.95-5 17 (2H, m, CH_2=), 5 62-5 75 (1H, m, -CH=), 7 34-7 49 (6H, m, Ar), 7 64-7 73 (4H, m, Ar), δ_C (100 MHz, $CDCl_3$) 10 27, 10 31 (CH_3), 19 35, 19.46 (CH_2), 25 13, 25 17 ($C(CH_3)_3$), 27 08 [$C(CH_3)_3$ of both diastereoisomers], 38 22, 38 54 (CH_2), 67.52, 69 27, 75 59, 76 06, 76 38 (3 x CH-O of 2 diastereoisomers), 113 67, 113 87 (CH_2=), 127 77, 128.84, 129 97, 130 03, 133 41, 133 51, 135 77, 135 87 (Ar), 140 97, 141 24 (=CH), *m/z* (EI) 341 (*M*-*t*-Bu, 0 2%), 339 (*M*-C_3H_7O, 0 6), 323 (*M*-*t*-Bu-H_2O, 7), *m/z* (CI, NH_3) 416 [$(M+NH_4)^+$, 2%], 399 [$(M+H)^+$, 13], (Found C, 72 5, H, 8 8 $C_{24}H_{34}O_3Si$ requires C, 72 3, H, 8 6%)

2(R,S*)-Phenylselenomethyl-4(S*)-ethyl-5(R*)-tert-butyldiphenylsilyloxy-7(R*,S*)-vinyl-1,3-dioxepane* **12**

The diol **5** (5 96 g, 14 9 mmol) was heated under reflux in dry toluene (150 ml) with 2-phenylselenoacetaldehyde diethylacetal[16,20] (4 52 g, 16 5 mmol) and PPTS (113 mg) for 2 5 hours The solution was allowed to cool, and was then poured into water (200 ml), and the aqueous phase was extracted with ether (3 x 500 ml) The extracts were washed with brine (500 ml), combined and dried The residue after removal of the solvent was chromatographed (10% ether in hexane) to yield the title *selenide* **12**, as a yellow oil (8 67 g, 100%), R_f (10% ether/hexane) 0 36/0 43, ν_{max} (CCl_4) 3070m, 2960s, 2930s, 2880m, 2860m (C-H stretches) cm^{-1}, The ^1H & ^{13}C NMR spectra were consistent with a complex mixture of diastereoisomers of the

required structure, *m/z* (CI, NH_3) 598 [$(M+NH_4)^+$, ^{80}Se, 14%], 398 (91), (Found C, 66 7, H, 7 0 $C_{32}H_{40}O_3SeSi$ requires C, 66 3, H, 7 0%)

*8(*R*)-tert-Butyldiphenylsilyloxy-9(*S*)-ethyl-4,7,8,9-tetrahydro-2(3H)-oxoninone* **3**

The selenide **12** (2 23 g, 3 85 mmol) was dissolved in methanol (280 ml) and water was added (40 ml) Sodium hydrogen carbonate (0 36 g, 4 29 mmol) then sodium metaperiodate (2 47 g, 11 5 mmol) were added and the resultant mixture was stirred for 90 minutes, giving a white precipitate The mixture was poured into water (1400 ml) and extracted with dichloromethane (3 x 500 ml) The combined extracts were dried over sodium sulphate, filtered, evaporated and dried under high vacuum to give a quantitative yield of the corresponding selenoxide

The selenoxide was dissolved in dry toluene (385 ml) and DBU (1 73 ml, 11 6 mmol) was added The solution was heated under reflux overnight (20 hours), allowed to cool and concentrated to a small volume The residue was purified by flash chromatography (hexane then 10% ether in hexane) to give the title *lactone* **3** as a colourless oil (1 52 g, 93%), R_f (10% ether/hexane) 0 30, ν_{max} (CCl_4) 1735vs (C=O) cm^{-1}, δ_H (250 MHz, $CDCl_3$) 0 81 (3H, t, *J* 7 Hz, CH_3), 1 04 (9H, s, $C(CH_3)_3$), 1 26-1 45 (1H, m, CH_2), 1 72-1 90 (1H, m, CH_2), 2 12-2 36 (6H, m, 2 x allylic CH_2 and CH_2CO), 3 68 (1H, m, CH-O), 4 84 (1H, dt, *J* 2, 9 Hz, CH-O), 5 30 (1H, m, CH=), 5 47 (1H, m, CH=), 7 40 (6H, m, PhH), 7 67 (4H, m, Ar), δ_C (100 MHz, $CDCl_3$) 9 48 (CH_3), 19 3, 23 9, 25 7 (2 x CH_2 and $C(CH_3)_3$), 26 9 [$C(CH_3)_3$], 33 8, 34 1 (2 x CH_2), 76 2, 80 8 (2 x CH-O), 127 3, 127 6, 127 7, 129 7, 129 7, 129 9, 133 3, 135 9, 135 9 (CH=CH and Ar), 174 7 (C=O), *m/z* (EI) 287 (*M*-*t*-Bu-Ph, 93%), 269 (*M*-2Ph, 86), *m/z* (CI, NH_3) 423 [$(M+H)^+$, 72%], 345 (*M*-Ph, 66), (Found C, 73 7, H, 8 0 $C_{26}H_{34}O_3Si$ requires C, 73 9, H, 8 1%)

ACKNOWLEDGEMENTS

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