Silicon-mediated Annulation. Part 2.[1] A Synthesis of β-Alkoxy Cyclo-octanones *via* Intramolecular Directed Aldol Reactions†

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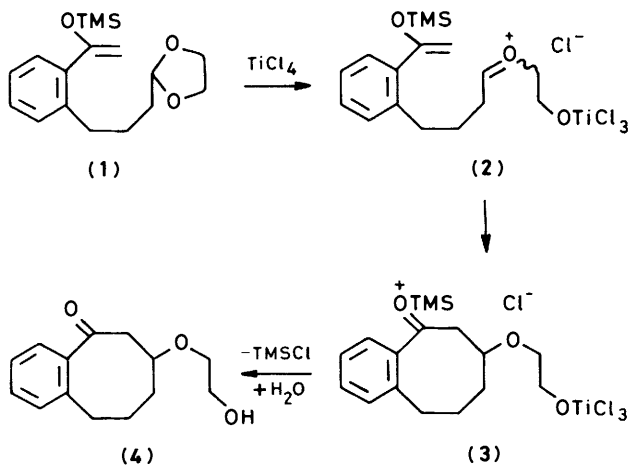
β-Alkoxycyclo-octanones were formed in poor to moderate yield by a Lewis acid-catalysed intramolecular directed aldol reaction between an acetal and an enol silane. From 10 examples, the effect of chain substitution, Lewis acid, and acetal structure on the efficiency of the 8-*exo*$_e$*endo*$_n$ cyclisations was examined. The beneficial effect of *gem*-dimethyl substitution is discussed.

The construction of medium rings from acyclic bifunctional precursors is difficult because intermolecular reactions compete favourably with the desired intramolecular reaction except at very high dilution. Medium ring annulations are usually thwarted by (*a*) the entropy loss upon formation of a ring-like transition state and (*b*) the adverse effects of imperfect staggering and transannular interactions as the linear precursor approaches the geometry of the transition state.[2] In view of these impediments the successful 8-*endo*$_e$*endo*$_n$ cyclisations leading to oxocan-4-ones reported in Part 1[1] seemed to us rather '... like a dog's walking on his hind legs. It is not done well; but you are surprised to find it done at all'.[3] In this paper[4] we show that the analogous 8-*exo*$_e$*endo*$_n$ cyclisations of enol silanes and acetals to give β-alkoxy-cyclo-octanones also occur in poor to moderate yield *via* intramolecular Mukaiyama directed aldol reactions[5] *without recourse to high dilution.*

The general reaction under discussion is exemplified by the conversion of enol silane (**1**) into the β-alkoxy benzocyclo-octanone (**4**) (Scheme 1) on treatment of (**1**) with 1.1 equiv. of



Scheme 1.

$TiCl_4$ in CH_2Cl_2 at −78 °C. The reaction was complete in 15 min at 0.1M concentration and gave (**4**) in 56% isolated yield. Although the mechanism of the Mukaiyama directed aldol reaction has not been examined in detail,‡ recent evidence suggests that the enol silane rather than the trichlorotitanium enolate[7] serves as the nucleophilic partner since enol silanes do not react with $TiCl_4$ at an appreciable rate at −78 °C. According to the mechanism outlined in Scheme 1, ring closure involves nucleophilic addition to an electrophilic oxonium ion; however, an alternative mechanism involving nucleophilic substitution of a polarised C–O bond of the acetal moiety would also lead to (**4**).[8] We believe that the addition mode is more likely with the highly oxyphilic $TiCl_4$.

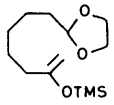
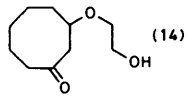
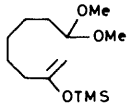
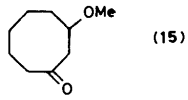
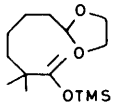
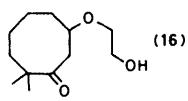
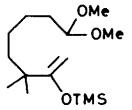
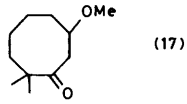
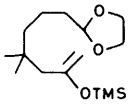
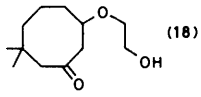
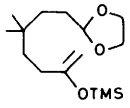
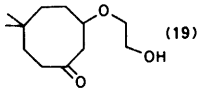
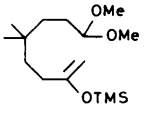
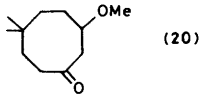
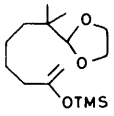
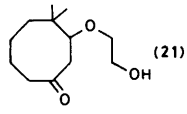
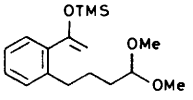
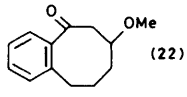
The conversion (**1**) ⟶ (**4**) is not a good indication of the potential of the directed aldol route to medium rings because the comparatively good yield probably reflects the reduced conformational mobility and transannular interactions resulting from the presence of the aromatic ring. Evidence to support this view comes from the $TiCl_4$–catalysed cyclisation of the enol silanes (**5**) and (**6**) (Table 1) to the cyclo-octanones (**14**) and (**15**) in a disappointing 12—13% yield. However, the analogous α-*gem*-dimethyl substituted enol silanes (**7**) and (**8**) underwent $TiCl_4$-catalysed cyclisation to the cyclo-octanones (**16**) and (**17**) in 43 and 33% yield respectively.

In an attempt to optimise reaction conditions the cyclisation of enol silanes (**7**) and (**8**) was examined with a variety of Lewis acids and the results are given in Table 1. In general the reactions were clean—even when the yields were low—because the principal by-products of the reaction were polymeric and easily separable from the desired products by chromatography. Reactions catalysed by $TiCl_4$ were virtually instantaneous at −78 °C whereas other catalysts required higher temperatures and longer reaction times. As in the earlier study,[1] $TiCl_4$ was uniformly successful in promoting the desired reaction but it did not always give the best yields. The best yield of all the examples studied was obtained by reaction of (**8**) with BF_3–Et_2O which gave (**17**) in 67% yield along with 7% of the dimer (**23**). Similarly, a good yield (69% total) of cyclisation products was obtained from the $TiCl_2(OPr^i)_2$-catalysed cyclisation of (**7**) since the expected product (**16**) (45%) was accompanied by 24% of the β-isopropoxycyclo-octanone (**24**). The latter compound probably arose from cyclisation of enol silane (**25**) generated by $TiCl_2(OPr^i)_2$-catalysed acetal exchange. The high yield obtained using the combination of BF_3–Et_2O and the dimethyl acetal in the cyclisation of the enol silane (**8**) was unique; in general, no advantage was derived from using the less stable dimethyl acetals rather than the dioxolanes. Trimethylsilyl (TMS) enol silanes were used throughout these studies and no attempt was made to examine the influence of silicon substitution on the course of the reaction.

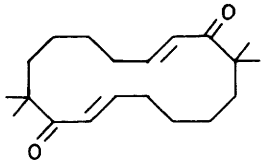
The dramatic improvement in yield in the cyclisation of (**7**) and (**8**) compared with their demethyl analogues (**5**) and (**6**) appears to be a clear example of the *gem*-dimethyl effect. This effect has been extensively studied in common rings[9] but its

† All compounds reported are racemic.
‡ The stereochemistry of the related Lewis-acid-catalysed reaction of enol silanes with aldehydes has recently been examined.[6]

Table 1. β-Alkoxycyclo-octanones *via* intramolecular Mukaiyama directed aldol reactions.

Enol silane	Lewis acid[a]	Temperature (°C)	Time	Yield (%)[b]	Product
(5) 	$TiCl_4$	−78	15 min	13	 (14)
(6) 	$TiCl_4$	−78	15 min	12	 (15)
(7) 	$TiCl_4$	−78	15 min	43	 (16)
	$TiCl_2(OPr^i)_2$	−78—25	20 h	45	
	BF_3–OEt_2	−78—25	20 h	48	
	$ZnBr_2$[c]	25	7 days	41	
	$SnCl_4$	−40	20 h	35	
	$CF_3SO_3SiMe_3$	−78—25	20 h	16	
(8) 	BF_3–OEt_2	−78—25	20 h	67	 (17)
	$TiCl_4$	−78	15 min	33	
	$ZnBr_2$	25	7 days	36	
(9) 	$TiCl_4$	−78	15 min	23	 (18)
(10) 	$TiCl_4$	−78	15 min	37	 (19)
	$TiCl_2(OPr^i)_2$	25	36 h	0	
	$TiCl(OPr^i)_3$[c]	−78—25	1 h	12	
(11) 	BF_3–OEt_2	−78—25	16 h	23	 (20)
	$TiCl_4$	−78	15 min	21	
(12) 	$TiCl_4$	−78	15 min	17	 (21)
(13) 	$TiCl_4$	−78	15 min	38	 (22)

[a] 1.1—1.2 Equiv. in CH_2Cl_2. Reactant concentration 0.05—0.1M. [b] Isolated yield after column chromatography and bulb-to-bulb distillation. [c] 2.2 Equiv.



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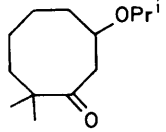

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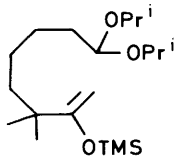
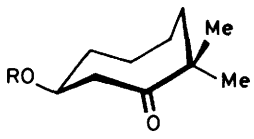


(25)

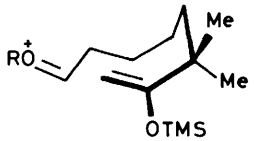
influence in promoting medium ring annulations has been postulated[10] and analysed.[11] In an attempt to assess the magnitude of the scope of the *gem*-dimethyl effect in promoting 8-*exo*$_e$*endo*$_n$ annulations, the cyclisation of the enol silanes (**9**)—(**12**) was examined. From the results shown in Table 1 it can be seen that the effect was at a maximum in the α-*gem*-dimethyl enol silanes (**7**) and (**8**), diminished but still significant in the $TiCl_4$-catalysed cyclisation of (**10**), and negligible in the case of (**9**), (**11**), and (**12**).

Based on a conformational analysis of the β-alkoxycyclo-octanone products, these results can be interpreted if we assume a ring-like transition state geometry which approximates the lowest energy conformation of the products. The α-*gem*-dimethylcyclo-octanones (**7**) and (**8**) should exist in the chair–boat conformation[12] (**26**) with the methyl groups occupying the

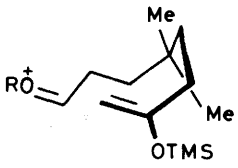
preferred 'corner site'[13] in which case the corresponding transition state geometry (**27**) should be particularly favourable since the beneficial effects of the methyl groups would not be compromised by any destabilising transannular interactions. Similarly, a favourable chair–boat transition state geometry (**28**) with 'corner site' methyl groups can be postulated for the cyclisation to the cyclo-octanones (**19**) and (**20**). However, in the case of the enol silanes (**9**) and (**12**), the *gem*-dimethyl substituents prohibit chair–boat transition state geometries (**29**) and (**30**) and cyclisation is forced to proceed through higher energy conformations[14] with an attendant diminution in yield.



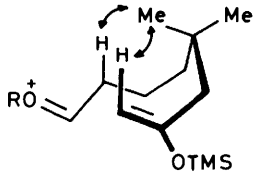
(**26**)



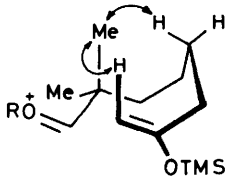
(**27**)



(**28**)



(**29**)



(**30**)

The circuitous methods recently employed for the construction of cyclo-octane rings testifies to the relative inaccessibility of 8-membered rings by direct ring closure of acyclic precursors.[15,16] Thus the 8-*exo*$_e$*endo*$_n$ cyclisations of the bifunctional saturated chains achieved *via* intramolecular directed aldol reactions reported herein are significant—despite their modest yield. That the reactions proceeded rapidly at − 78 °C and at 0.1M concentration suggests the intervention of powerful factors for promoting the cyclisations. From the results reported above it appears that strategically placed substituents play an important role by influencing the ground state conformation of the reactant. A second factor which also reduces the entropy of the reaction is a template effect in which $TiCl_4$—the most generally successful of the Lewis acids tried—co-ordinates one of the acetal oxygens and the enol silane oxygen. Although a template effect may be necessary for some of the cyclisations, its implication is not obligatory since the mono-co-ordinate Lewis acid BF_3–Et_2O was equally effective in some cases. The relative efficiency of the cyclisation of α-*gem*-disubstituted enol silanes (**7**) and (**8**) is noteworthy and suggests the potential of using removable, strategically placed functional auxiliaries specifically intended for promoting difficult medium ring annulations.

Experimental

For general experimental details see ref. 1. The enol silanes were prepared as shown in Scheme 2. Since standard procedures were used throughout, only the physical constants of the products are cited. ^{13}C N.m.r. data for the β-alkoxycyclo-octanones are given in Table 2. For a general procedure for the cyclisations see ref. 1.

2-(1,1-*Dimethylbut*-3-*enyl*)-1,3-*dioxolane* (**32**).—From aldehyde (**31**) (10 g, 89 mmol) and ethylene glycol (6.2 g, 100 mmol) was obtained (**32**) (11.3 g, 72 mmol, 81%) after distillation; b.p. 115 °C (bath)/15 mmHg; $\nu_{max.}$ 1 640m and 1 115s cm^{-1}; δ_H 5.8 (1 H, m), 5.0 (2 H, m), 4.42 (1 H, s), 3.8 (4 H, m); 2.05 (2 H, dd, *J* 8, *J'* < 1), and 0.85 (6 H, s).

2-(4-*Hydroxy*-1,1-*dimethylbutyl*)-1,3-*dioxolane* (**33**).—Hydroboration[17] of (**32**) (5.5 g, 35 mmol) with BH_3–Me_2S (1.6 cm^3, 16 mmol) gave crude alcohol (**33**) (6.2 g) [δ_H 4.54 (1 H, s), 3.9 (4 H, m), 3.6 (2 H, m), 3.5 (1 H, s, OH), 1.21—1.9 (4 H, m), and 0.90 (6 H, s)] which was used in the next step without further purification.

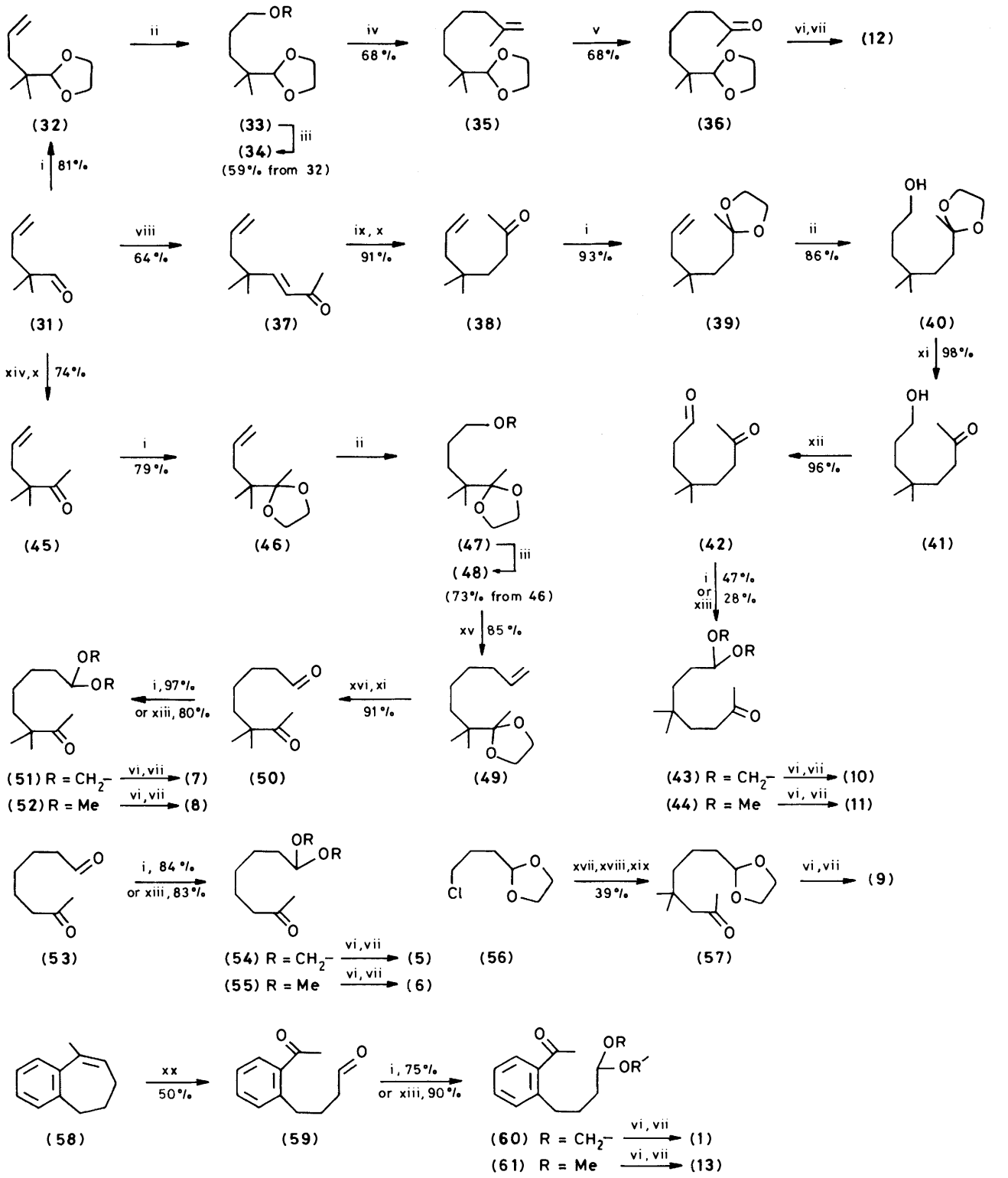
2-[1,1-*Dimethyl*-4-(p-*tolylsulphonyloxy*)*butyl*]-1,3-*dioxolane* (**34**).—From crude alcohol (**33**) (6.1 g) was obtained the toluene-*p*-sulphonate (**34**) (6.2 g, 21 mmol, 59%) as a gum after column chromatography (6 × 5 cm, 10% Et_2O in benzene); $\nu_{max.}$ 1 600m, 1 360s, 1 180s, and 1 110s cm^{-1}; δ_H 7.74 and 7.30 (2 H each, d, *J* 8), 4.38 (1 H, s), 3.90 (2 H, t, *J* 7), 3.8 (4 H, m), 2.46 (3 H, s), 1.6 (2 H, m), 1.2 (2 H, m), and 0.82 (6 H, s) (Found: M^+, 328.134 27. $C_{16}H_{24}O_5S$ requires *M*, 328.134 435).

2-(1,1,6-*Trimethylhept*-6-*enyl*)-1,3-*dioxolane* (**35**).—Reaction of the toluene-*p*-sulphonate (**34**) (3.14 g, 10.6 mmol) with the Grignard reagent prepared in THF in the usual way from 2-methylallyl chloride (2.8 cm^3, 27 mmol) in the presence of Li_2CuCl_4 (0.18 mmol) according to the procedure of Tamura and Kochi[18] gave the alkene (**35**) (1.52 g, 7.18 mmol, 68%) after column chromatography (5 × 2.5 cm, 5% Et_2O in benzene) and distillation, b.p. 110 °C (bath)/0.2 mmHg; $\nu_{max.}$ 1 640m, and 1 110s cm^{-1}; δ_H 4.7 (2 H, m), 4.54 (1 H, s), 3.9 (4 H, m), 2.0 (2 H, m), 1.62 (3 H, s), 1.3 (6 H, m), and 0.90 (6 H, s) (Found: M^+, 212.177 12. $C_{13}H_{24}O_2$ requires *M*, 212.177 620).

2-(1,1-*Dimethyl*-6-*oxoheptyl*)-1,3-*dioxolane* (**36**).—Oxidation of the alkene (**35**) (2.12 g, 10 mmol) with OsO_4 (24 mg) and $NaIO_4$ (4.65 g) in 3:1 dioxane–water (44 cm^3) as described[19] gave the ketone (**36**) (1.46 g, 6.8 mmol, 68%) after column chromatography (6 × 4 cm, 4% Et_2O in light petroleum) and distillation, b.p. 120 °C (bath)/0.15 mmHg; $\nu_{max.}$ 1 715s and 1 110s cm^{-1}; δ_H 4.51 (1 H, s), 3.9 (4 H, m), 2.46 (2 H, t, *J* 7), 2.13 (3 H, s), 1.2—1.7 (6 H, m), and 0.90 (6 H, s) (Found: M^+, 214.156 85. $C_{12}H_{22}O_3$ requires *M*, 214.156 885).

3-(2-*Hydroxyethoxy*)-4,4-*dimethylcyclo-octan*-1-*one* (**21**).—The ketone (**36**) (642 mg, 3.0 mmol) was converted into the lithium enolate with lithium di-isopropylamide (1.8 equiv.) in THF at −78 °C and silylated with chlorotrimethylsilane (6 equiv.) as described by House and co-workers.[20] The mixture was warmed to room temperature, filtered, concentrated under reduced pressure, and the residue treated with pentane and filtered. The solvent was removed under reduced pressure and the residue stored at 40 °C, 0.1 mmHg for 1 h whereupon the crude enol silane (**12**), contaminated with di-isopropylamine was used immediately in the next step. Control experiments showed that enol silanes freed of di-isopropylamine fared no better in the subsequent cyclisation step. This same procedure was used to prepare enol silanes (**1**) and (**5**)—(**13**).

Treatment of enol silane (**12**) (1.49 g) in CH_2Cl_2 (30 cm^3) with $TiCl_4$ (1.2 equiv.) at −78 °C for 15 min and work-up as previously described,[1] gave (**21**) after column chromatography (5 × 2 cm, 10—40% Et_2O in benzene) and distillation, b.p.



Scheme 2. *Reagents:* i, ethylene glycol, H^+; ii, BH_3–Me_2S–THF followed by H_2O_2–NaOH; iii, toluene-*p*-sulphonyl chloride–pyridine; iv, 2-methylprop-2-enylmagnesium chloride–Li_2CuCl_4–THF; v, OsO_4–$NaIO_4$–dioxane–H_2O; vi, Pr^i_2NLi–THF; vii, excess Me_3SiCl–THF; viii, acetone–NaOEt–EtOH; ix, Li–NH_3(l)–EtOH; x, H_2CrO_4–H_2O–Et_2O; xi, H_3O^+–THF; xii, Me_2SCl_2–Et_3N–CH_2Cl_2; xiii, $CeCl_3 \cdot 7H_2O$–$HC(OMe)_3$–MeOH; xiv, MeMgI–Et_2O; xv, allylmagnesium bromide–Li_2CuCl_4–THF; xvi,, O_3–MeOH followed by $(MeO)_3P$; xvii, Mg–THF; xviii, CuBr–Me_2S–THF–Et_2O–Me_2S; xix, 4-methylpent-3-en-2-one; xx, O_3–MeOH followed by Me_2S.

180 °C (bath)/0.35 mmHg; $\nu_{max.}$ 1 695s and 1 110s cm^{-1}; δ_H 3.7 (5 H, m), 2.45 (1 H, s, OH), 2.1—2.7 (4 H, m), 1.1—1.9 (6 H, m), and 1.07 and 0.90 (3 H each, s) (Found: M^+, 214.157 03. $C_{12}H_{22}O_3$ requires M, 214.156 885).

5,5-*Dimethylocta*-3,7-*dien*-2-*one* (**37**).—A mixture of the aldehyde (**31**) (23 g, 0.21 mol) and acetone (100 cm^3) was added to a solution of sodium ethoxide (0.15 mol) in EtOH (420 cm^3) and the mixture was stirred at 20 °C for 5 h. Water (100 cm^3) was added and the bulk of the solvent evaporated. The residue was extracted with Et_2O (2 × 100 cm^3) and the combined extracts washed with water, dried, and concentrated. Fractional distillation of the residue gave the enone (**37**) (20.1 g, 0.135 mol, 64%), b.p. 104—108 °C/15 mmHg; $\lambda_{max.}$($CHCl_3$) 316.5 nm (ε 102) and 243.5 nm (ε 4 650); $\nu_{max.}$ 1 675s and 1 620s cm^{-1}; δ_H 7.88 (1 H, d, *J* 16), 6.01 (1 H, d, *J* 16), 5.79 (1 H, ddt, *J* 7, *J'* 16, *J''* 11 Hz), 5.01 (2 H, m), 2.28 (3 H, s), 1.96 (2 H, dd, *J* 7, *J'* 1), and 1.05 (6 H, s) (Found: M^+, 152.119 87. $C_{10}H_{16}O$ requires M, 152.120 109).

5,5-*Dimethyloct*-7-*en*-2-*one* (**38**).—Lithium shot was added in portions to a solution of the enone (**37**) (20.1 g, 0.134 mol), Et_2O (50 cm^3), and EtOH (10 cm^3) in ammonia (250 cm^3) at −78 °C until the blue colour persisted. After 1 h sufficient EtOH was added to destroy the blue colour and the cooling bath was removed. An Et_2O solution of the residue obtained on evaporation of the solvent was washed with water, dried, and evaporated. The resultant oil in Et_2O (50 cm^3) was oxidised by the procedure of Brown and Garg[21] with aqueous H_2CrO_4 (1.4M; 65 cm^3) to give the ketone (**38**) (18.8 g, 0.122 mol, 91%) after short path distillation, b.p. 80—85 °C/15 mmHg; $\nu_{max.}$ 1 710s cm^{-3}; δ_H 5.79 (1 H, ddt, *J* 7, *J'* 15, *J''* 11 Hz), 5.0 (2 H, m), 2.4 (2 H, m), 2.15 (3 H, s), 1.96 (2 H, dd, *J* 7, *J'* 1), 1.5 (2 H, m), and 0.88 (6 H, s) (Found: M^+, 154.135 34. $C_{10}H_{18}O$ requires M, 154.135 758).

2-(3,3-*Dimethylhex*-5-*enyl*)-2-*methyl*-1,3-*dioxolane* (**39**).—Reaction of the ketone (**38**) (4.22 g, 27.4 mmol) with ethylene glycol (4 g, 70 mmol) in refluxing benzene (40 cm^3) containing p-TsOH·H_2O (10 mg) gave the acetal (**39**) (4.49 g, 22.7 mmol, 93%) after distillation, b.p. 120 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 640 cm^{-1}; δ_H 5.79 (1 H, ddt, *J* 7, *J'* 15, *J''* 11), 5.0 (2 H, m), 4.91 (4 H, br s), 1.97 (2 H, dd, *J* 8, *J'* 1), 1.55—1.75 (2 H, m), 1.31 (3 H, s), 1.1—1.4 (2 H, m), and 0.87 (6 H, s) (Found: M^+, 198.162 13. $C_{12}H_{22}O_2$ requires M, 198.161 971).

2-(6-*Hydroxy*-3,3-*dimethylhexyl*)-2-*methyl*-1,3-*dioxolane* (**40**).—Hydroboration[17] of (**39**) (2.38 g, 12 mmol) in THF gave the alcohol (**40**) (2.24 g, 10.35 mmol, 86%) after distillation, b.p. 150 °C (bath)/0.2 mmHg; $\nu_{max.}$ 3 410m and 1 060s cm^{-1}; δ_H 3.90 (4 H, br s), 3.69 (2 H, t, *J* 5), 1.1—1.9 (8 H, m), 1.74 (1 H, s, OH), 1.30 (3 H, s), and 0.87 (6 H, s) (Found: M^+, 216.172 66. $C_{12}H_{24}O_3$ requires M, 216.172 534).

8-*Hydroxy*-5,5-*dimethyloctan*-2-*one* (**41**).—Hydrolysis of the acetal (**40**) (6.14 g, 26.6 mmol) in THF–H_2O (4:11, 65 cm^3) containing *p*-TsOH·H_2O (60 mg) gave the ketone (**41**) (4.54 g, 26.3 mmol, 98%) after distillation, b.p. 120 °C (bath)/0.1 mmHg; $\nu_{max.}$ 3 400s and 1 705s cm^{-1}; δ_H 3.61 (2 H, t, *J* 7), 2.40 (2 H, t, *J* 8), 2.14 (3 H, s), 1.73 (1 H, s, OH), 1.1—1.7 (6 H, m), and 0.87 (6 H, s) (Found: M^+, 172.145 67. $C_{10}H_{20}O_2$ requires M, 172.146 32).

4,4-*Dimethyl*-7-*oxo*-*octanal* (**42**).—Oxidation of the alcohol (**41**) (1.0 g, 5.8 mmol) by the method of Swern and co-workers[22] gave the keto aldehyde (**41**) (5.6 mmol, 96%) after distillation, b.p. 100 °C (bath)/0.05 mmHg; $\nu_{max.}$ 1 710s; δ_H 9.76 (1 H, t, *J ca.* 1), 2.42 (4 H, dt, *J* 8, *J'* 1), 2.14 (3 H, s), 1.5 (4 H, m), and 0.87 (6 H, s) (Found: M^+, 170.130 54. $C_{10}H_{18}O_2$ requires M, 170.130 672).

8,8-*Dimethyoxy*-5,5-*dimethyloctan*-2-*one* (**44**).—The keto aldehyde (**42**) (1.96 g, 11.5 mmol) in MeOH was converted into the dimethyl acetal (**43**) in the presence of $HC(OMe)_3$ (5 equiv.) and $CeCl_3$·$7H_2O$ (1 equiv.) as described.[23] The keto acetal (**44**) (692 mg, 3.3 mmol, 28%) was obtained after column chromatography (5 × 2 cm, 8% Et_2O in light petroleum) and distillation, b.p. 100 °C (bath)/0.03 mmHg; $\nu_{max.}$ 1 695s and 1 090s cm^{-1}; δ_H 4.92 (1 H, t, *J* 5), 3.30 (6 H, s), 2.36 (2 H, t with fine splitting, *J* 8, *J' ca.* 1), 2.13 (3 H, s), 1.0—1.7 (6 H, m), and 0.84 (6 H, s).

3-*Methoxy*-6,6-*dimethylcyclo*-*octanone* (**20**).—The ketone (**44**) (330 mg, 1.50 mmol) was converted into the enol silane and cyclised in CH_2Cl_2 (20 cm^3) with $TiCl_4$ (1.1 equiv.) to give (**20**) (58.5 mg, 0.318 mmol, 21%) after column chromatography (4 × 2 cm, 10% Et_2O in light petroleum) and distillation, b.p. 100 °C (bath)/0.6 mmHg; $\nu_{max.}$ 1 695s cm^{-1}; δ_H 3.36 (3 H, s), 3.3 (1 H, m), 2.77 (1 H, dd, *J* 11, *J'* 11), 2.68 (1 H, ddd, *J* 11, *J'* 4, *J''* 1), 2.44 (1 H, dd, *J* 4, *J'* 8), 2.33 (1 H, dd, *J* 4, *J'* 2), 1.8—2.25 (2 H, m), 1.1—1.8 (4 H, m), 1.55 (1 H, s, OH), and 0.91 and 0.88 (3 H each, s) (Found: M^+, 184.145 96. $C_{11}H_{20}O_2$ requires M, 184.146 321).

2-(3,3-*Dimethyl*-6-*oxoheptyl*)-1,3-*dioxolane* (**43**).—Reaction of the keto aldehyde (**42**) (960 mg, 5.58 mmol) with ethylene glycol (372 mg, 6 mmol) in benzene (10 cm^3) containing *p*-TsOH·H_2O (10 mg) gave the dioxolane (**43**) (567 mg, 2.65 mmol, 47%) after column chromatography (8 × 2.5 cm, 4—30% Et_2O in light petroleum) and distillation, b.p. 110 °C (bath)/0.4 mmHg; $\nu_{max.}$ 1 715s and 1 040 cm^{-1}; δ_H 4.80 (1 H, t, *J* 4), 3.9 (4 H, m), 2.4 (2 H, m), 2.16 (3 H, s), 1.1—1.8 (6 H, m), and 0.87 (6 H, s) (Found: M^+, 214.1567. $C_{12}H_{22}O_3$ requires M, 214.156 885).

3-(2-*Hydroxyethoxy*)-6,6-*dimethylcyclo*-*octanone* (**21**).—Cyclisation of the enol silane (**12**) prepared from the dioxolane (**43**) (442 mg, 2.06 mmol) with $TiCl_4$ gave (**21**) (172 mg, 0.804 mmol, 39%) after column chromatography (4 × 2 cm, 5—60% Et_2O in light petroleum) and distillation, b.p. 150 °C (bath)/0.6 mmHg; $\nu_{max.}$ 3 420s, 1 690s, and 1 060s cm^{-1}; δ_H 3.7 (4 H, m), 3.6 (1 H, m), 2.77 (1 H, dd, *J* 11, *J'* 10), 2.64 (1 H, d, *J* 11), 2.63 (1 H, s, OH), 2.42 (1 H, dd, *J* 7, *J'* 5), 2.42 (1 H, dd, *J* 7, *J'* 7), 1.2—2.25 (6 H, m), and 0.91 and 0.90 (3 H each, s) (Found: M^+, 214.156 71. $C_{12}H_{22}O_3$ requires M, 214.156 885).

3,3-*Dimethylhex*-5-*en*-2-*one* (**45**).—Reaction of the aldehyde (**31**)[24] (10.34 g, 92 mmol) with the Grignard reagent prepared from iodomethane (8.3 cm^3, 138 mmol) and Mg (4.44 g, 185 mmol) in Et_2O (120 cm^3) gave 3,3-dimethylhex-5-en-2-ol (12 g, 91%). A portion (7.1 g, 55 mmol) in Et_2O (20 cm^3) was oxidised by the method of Brown and Garg[21] to give the ketone (**45**) (5.93 g, 47 mmol, 85%) after distillation, b.p. 95 °C (bath)/15 mmHg; $\nu_{max.}$ 1 705s and 1 640m cm^{-1}; δ_H 5.66 (1 H, ddt, *J* 15, *J'* 10, *J''* 7), 5.0 (2 H, m), 2.25 (2 H, dt, *J* 7, *J'* 2), 2.10 (3 H, s), and 1.10 (6 H, s); *m/z* 126 (M^+, 1.5%), 56 (100), 113 (15), 100 (13), 95 (21), 83 (18), 69 (39), and 43 (57).

2-*Methyl*-2-(1,1-*dimethylbut*-3-*enyl*)-1,3-*dioxolane* (**46**).—Reaction of the ketone (**45**) (2.8 g, 23 mmol) with ethylene glycol (1.55 g, 25 mmol) and *p*-TsOH·H_2O (10 mg) in refluxing benzene for 48 h gave the dioxolane (**46**) (2.94 g, 17.3 mmol, 79%), after distillation; b.p. 100 °C (bath)/15 mmHg; $\nu_{max.}$ 1 640m, 1 050s, and 890 cm^{-1}; δ_H 5.85 (1 H, ddt, *J* 15, *J'* 10, *J''* 7), 5.0 (2 H, m), 3.9 (4 H, m), 2.15 (2 H, dd, *J* 7, *J'* 2), and 1.24 (3 H, s), 0.92 (6 H, s).

2-(4-*Hydroxy*-1,1-*dimethylbutyl*)-2-*methyl*-1,3-*dioxolane* (**47**).—Hydroboration[17] of the alkene (**46**) (3.81 g, 18.7 mmol) in THF with BH_3–Me_2S (0.67 cm^3, 6.7 mmol) gave the crude alcohol (**47**) (4.28 g) which was used directly in the next step. A purified sample gave δ_H 3.91 (4 H, m), 3.61 (2 H, t, *J* 7), 2.0 (1 H, s, OH), 1.1—1.65 (4 H, m), 1.25 (3 H, s), and 0.94 (6 H, s) (Found: M^+, 188.140 96. $C_{10}H_{20}O_3$ requires *M*, 188.141 235).

2-[1,1-*Dimethyl*-4-(p-*tolylsulphonyloxy*)*butyl*]-2-*methyl*-1,3-*dioxolane* (**48**).—Tosylation of the crude alcohol (**47**) (4.28 g) in the usual way gave the toluene-*p*-sulphonate (**48**) (4.80 g, 14.03 mmol, 73% overall) as white needles, m.p. 44.5—45.6 °C (MeOH–water) (Found: C, 59.75; H, 7.65. $C_{17}H_{26}O_5S$ requires C, 59.65; H, 7.89%).

2-(1,1-*Dimethylhept*-6-*enyl*)-2-*methyl*-1,3-*dioxolane* (**49**).—Reaction of the toluene-*p*-sulphonate (**48**) (4.08 g, 11.9 mmol) with an excess of allylmagnesium bromide in THF in the presence of Li_2CuCl_4 according to Tamura and Kochi,[18] gave the alkene (**49**) (2.15 g, 10.1 mmol, 85%) after chromatography (5 × 4.5 cm, 5% Et_2O in light petroleum) and distillation, b.p. 90 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 640m and 1 050s cm^{-1}; δ_H 5.84 (1 H, ddt, *J* 14, *J'* 8, *J''* 6), 4.95 (2 H, m), 3.9 (4 H, m), 2.1 (2 H, m), 1.35 (6 H, m), 1.24 (3 H, s), and 0.91 (6 H, s) (Found: M^+, 212.177 52. $C_{13}H_{24}O_3$ requires *M*, 212.177 620).

6,6-*Dimethyl*-7-*oxo*-*octanal* (**50**).—Ozonolysis of the alkene (**49**) (7.0 g, 34 mmol) in MeOH (30 cm^3) followed by reductive work-up with $(MeO)_3P$[25] (10 cm^3) freshly distilled from Na gave an aldehyde (6.95 g) which was hydrolysed in THF–water (4:1) (60 cm^3) containing *p*-TsOH (30 mg) to give the keto aldehyde (**50**) (5.27 g, 30.9 mmol, 91%) after distillation, b.p. 100 °C (bath)/0.15 mmHg; $\nu_{max.}$ 1 705s and 1 725s cm^{-1}; δ_H 9.71 (1 H, t, *J* 1), 2.44 (2 H, dt, *J* 7, *J'* 1), 2.10 (3 H, s), 1.2—1.85 (6 H, m), and 1.09 (6 H, s) (Found: M^+, 170.130 46. $C_{10}H_{18}O_2$ requires *M*, 170.130 672).

2-(5,5-*Dimethyl*-6-*oxoheptyl*)-1,3-*dioxolane* (**51**).—Reaction of the keto aldehyde (**50**) (1.38 g, 8.1 mmol) with ethylene glycol (0.53 g, 8.5 mmol) in the usual way gave the dioxolane (**51**) (1.69 g, 7.9 mmol, 97%) after distillation, b.p. 100 °C (bath)/0.15 mmHg; $\nu_{max.}$ 1 705s and 1 030s cm^{-1}; δ_H 4.83 (1 H, t, *J* 6), 3.9 (4 H, m), 2.10 (3 H, s), 1.1—1.75 (8 H, m), and 1.09 (6 H, s) (Found: M^+, 214.156 51. $C_{12}H_{22}O_3$ requires *M*, 214.156 885).

3-(2-*Hydroxyethoxy*)-8,8-*dimethylcyclo*-*octanone* (**16**).—Cyclisation of the enol silane (**7**) prepared from the ketone (**51**) (567 mg, 2.65 mmol) with $TiCl_2(OPr^i)_2$ (1.1 equiv.) in CH_2Cl_2 (45 cm^3) at −78 °C for 1 h and then at room temperature overnight, gave two main products which were isolated by column chromatography (5 × 2 cm, 40—90% Et_2O in light petroleum). The first compound to elute was (**16**) (254 mg, 1.2 mmol, 45%); b.p. 150 °C (bath)/0.3 mmHg; $\nu_{max.}$ 3 440s, 1 695s, and 1 070s cm^{-1}; δ_H 3.7 (4 H, m), 3.7 (1 H, m), 3.14 (1 H, s, OH), 2.91 (1 H, dd, *J* 10, *J'* 11), 2.56 (1 H, dd, *J* 10, *J'* 4), 1.9—2.3 (2 H, m), 1.3—1.9 (6 H, m), and 1.08 (6 H, s) (Found: M^+, 214.156 88. $C_{12}H_{22}O_3$ requires *M*, 214.156 13); the second compound to elute was the cyclo-octanone (**24**) (134 mg, 0.61 mmol, 24%), b.p. 70 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 695s and 1 070s cm^{-1}; δ_H 3.72 (1 H, septet, *J* 6), 3.5 (1 H, m), 2.99 (1 H, dd, *J* 10.5, *J'* 10.5), 2.42 (1 H, ddd, *J* 10.5, *J'* 4, *J''* 1), 2.35—1.3 (8 H, m), 1.15 and 1.13 (3 H each, d, *J* 6), and 1.105 (6 H, s) (Found: M^+, 212.1778. $C_{12}H_{24}O_2$ requires *M*, 212.177 620).

8,8-*Dimethoxy*-3,3-*dimethyloctan*-2-*one* (**52**).—Selective protection of the keto aldehyde (**50**) (1.23 g, 7.23 mmol) by the method of Gemal and Luche[23] gave the keto acetal (**52**) (1.39 g, 6.44 mmol, 80%), $\nu_{max.}$ 1 690s and 1 090 cm^{-1}; δ_H 4.32 (1 H, t, *J* 6), 3.30 (6 H, s), 2.10 (3 H, s), 1.05—1.85 (8 H, m), and 1.10 (6 H, s).

3-*Methoxy*-8,8-*dimethylcyclo*-*octanone* (**17**).—Reaction of the enol silane (**8**) prepared from the ketone (**52**) (545 mg, 2.5 mmol) with BF_3–Et_2O (1.1 equiv.) gave the cyclo-octanone (**17**) (309 mg, 1.7 mmol, 67%) after column chromatography (5 × 2 cm; 10—40% Et_2O in light petroleum) and distillation, b.p. 100 °C (bath)/0.3 mmHg; $\nu_{max.}$ 1 690s and 1 095s cm^{-1}; δ_H 3.4 (1 H, m), 3.37 (3 H, s), 2.90 (1 H, dd, *J* 10.7, *J'* 10.7), 2.57 (1 H, ddd, *J* 10.5, *J'* 4.1, *J''* 1.3), 1.7—2.4 (2p, m), 1.25—1.7 (6 H, m), and 1.06 (6 H, s) (Found: M^+, 184.146 35. $C_{11}H_{20}O_2$ requires *M*, 184.146 321).

8,8,16,16-*Tetramethylcyclohexadeca*-2,10-*diene*-1,9-*dione* (**23**) (27 mg, 0.17 mmol, 7%) was also isolated, m.p. 148.9—150.1 °C ($CHCl_3$–light petroleum); $\lambda_{max.}$($CHCl_3$) 245.7 nm (ε 5 600); $\nu_{max.}$ 1 660s and 1 645m; δ_H 6.86 (2 H, dt, *J* 15, *J'* 8), 6.36 (2 H, dd, *J* 15, *J'* 1), 2.2 (4 H, m), 1.25—1.7 (12 H, m), and 1.12 (12 H, s); *m/z* 304 (M^+, 51%), 81 (100), 194 (23), 179 (30), 151 (46), 123 (41), 108 (98), 95 (60), 69 (61), 55 (84), and 43 (49) (Found: M^+, 304.239 96. $C_{20}H_{32}O_2$ requires *M*, 304.240 217). Compound (**23**) did not give a satisfactory combustion analysis.

2-(6-*Oxoheptyl*)-1,3-*dioxolane* (**54**).—The keto aldehyde (**53**)[26] (0.68 g, 3.76 mmol) was treated with ethylene glycol (0.23 g, 3.7 mmol) in CH_2Cl_2 (12 cm^3) containing *p*-TsOH·H_2O (10 mg) and anhydrous Na_2SO_4 (4 g) at 20 °C for 20 h to give the dioxolane (**54**) (0.574 g, 3.1 mmol, 84%) after distillation, b.p. 120 °C (bath)/0.3 mmHg; $\nu_{max.}$ 1 710s and 1 130m cm^{-1}; δ_H 4.92 (1 H, t, *J* 8); 3.9 (4 H, m), 2.42 (2 H, t, *J* 8), 2.12 (3 H, s), and 1.2—1.85 (8 H, m) (Found: M^+, 186.125 18. $C_{10}H_{18}O_3$ requires *M*, 186.125 586).

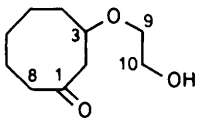
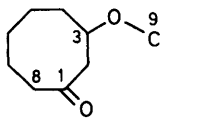
3-(2-*Hydroxyethoxy*)*cyclo*-*octanone* (**14**).—Reaction of enol silane (**5**) prepared from the ketone (**54**) (248 mg, 1.33 mmol) with $TiCl_4$ in the usual way gave the cyclo-octanone (**14**) (30 mg, 0.16 mmol, 12%) after distillation, b.p. 120 °C (bath)/0.2 mmHg; $\nu_{max.}$ 3 440m, 1 690s, and 1 110s cm^{-1}; δ_H 3.74 (1 H, m), 3.7 (4 H, m), 2.7 (2 H, m), 2.4 m), and 1.1—2.1 (9 H, m) (Found: M^+, 186.125 95. $C_{10}H_{18}O_3$ requires *M*, 186.125 586).

8,8-*Dimethoxyoctan*-2-*one* (**55**).—The keto aldehyde (**53**)[26] (400 mg, 2.82 mmol) was converted into the acetal (**55**) (452 mg, 2.40 mmol, 83%) by the method of Gemal and Luche,[23] $\nu_{max.}$ 1 710s, 1 125s, and 1 150s cm^{-1}; δ_H 4.32 (1 H, t, *J* 5, 3.31 (6 H, s), 2.43 (2 H, t, *J* 8), 2.13 (3 H, s), and 1.1—1.8 (8 H, m).

3-*Methoxycyclo*-*octanone* (**15**).—Reaction of the enol silane (**6**) prepared from the ketone (**55**) (452 mg, 2.4 mmol) with $TiCl_4$ in the usual way gave the cyclo-octanone (**15**) (51 mg, 0.34 mmol, 14%) after distillation, b.p. 80 °C (bath)/0.2 mmHg; $\nu_{max.}$ 1 695s and 1 100s cm^{-1}; δ_H 3.4 (1 H, m), 3.37 (3 H, s), 2.7 (2 H, m), 2.35 (2 H, m), and 1.4—1.7 (6 H, m) (Found: M^+, 156.115 34. $C_9H_{16}O_2$ requires *M*, 156.115 023).

2-(4,4-*Dimethyl*-6-*oxoheptyl*)-1,3-*dioxolane* (**57**).—A mixture of Mg (644 mg, 19 mmol), 1,2-dibromoethane (0.1 cm^3) and the chloride (**56**) (594 mg, 3.94 mmol) in THF (4 cm^3) was warmed to 35 °C with rapid stirring to initiate formation of the Grignard reagent. After 1 h at ambient temperature, the mixture was cooled to −78 °C and $CuBrMe_2S$ (0.3 g, 1.58 mmol) in Me_2S (3 cm^3) was added and the mixture stirred at −78 °C for 1 h. 4-Methylpent-3-en-2-one (620 mg, 6.3 mmol) in Et_2O (3 cm^3) was added dropwise and the mixture stirred at −78 °C for 1.5 h before being warmed to 0 °C. A mixture of 15M-NH_4OH and saturated aqueous NH_4Cl (1:4; 10 cm^3) was added and after vigorous gas evolution had ceased, extraction with Et_2O (3 × 50 cm^3) was followed by washing of the combined extracts with

Table 2. ^{13}C Chemical shifts[a] for β-alkoxycyclo-octanones.

Cyclo-octanone		Chemical shift (δ)												
		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Me_1	Me_2	Unassigned signals
	**(4)**	208.7	48.2	75.2	28.7	22.7	34.3	138.5	141.8	69.9	61.6	—	—	132.9, 131.9, 129.1, 126.5
	(14)	213.6	44.4	78.7	28.2	22.5	19.8	32.0	44.3	70.2	61.9	—	—	
	(16)	216.4	41.1	80.1	31.9	24.0	19.1	35.8	47.2	70.1	61.0	25.6	22.4	
	(18)	210.3	52.8	76.2	*b*	*b*	*b*	*b*	50.8	69.9	62.0	31.5	27.7	39.8, 36.1, 35.6, 18.9
	(19)	212.6	44.2	79.7	33.7	28.7	33.5	32.9	42.1	70.2	61.7	28.9	28.2	
	(21)	213.7	45.7	82.2	39.1	29.3	22.3	38.4	41.5	71.7	62.1	26.1	22.3	
	**(15)**	213.1	44.9	80.2	28.2	22.7	20.3	31.1	44.3	56.4	—	—	—	
	(17)	215.7	41.4	81.7	31.7	24.9	19.4	35.9	47.9	56.2	—	26.8	21.2	
	(20)	211.8	44.6	81.5	33.4	28.7	33.7	34.1	42.3	56.3	—	56.3	28.1	
	(22)	200.7	49.3	77.0	28.3	22.8	34.6	138.7	140.4	56.2	—	—	—	132.8, 131.7, 129.3, 126.7
	(24)	216.0	43.1	77.7	33.0	34.9	19.6	35.7	47.1	69.4	—	*b*	*b*	27.3, 23.0, 22.6, 20.6

[a] Recorded at 22.5 MHz in $CDCl_3$. [b] Insufficient information to permit assignment.

NH_4Cl and brine. The residue obtained after drying and evaporation was chromatographed (6 × 2.8 cm, 15—40% Et_2O in light petroleum) to give the keto acetal (**57**) (314 mg, 1.48 mmol, 39%) after distillation, b.p. 100 °C (bath)/0.4 mmHg; $\nu_{max.}$ 1 705s and 1 025s cm^{-1}; δ_H 4.98 (1 H, t, *J* 6), 4.0 (4 H, m), 2.40 (2 H, s), 2.18 (3 H, s), 1.3—1.7 (6 H, m), and 1.02 (6 H, s) (Found: M^+, 214.156 62. $C_{12}H_{22}O_3$ requires *M*, 214.156 885).

3-(2-*Hydroxyethoxy*)-7,7-*dimethylcyclo-octanone* (**18**).—Reaction of the enol silane (**9**) prepared from the ketone (**57**) (190 mg, 0.90 mmol) with $TiCl_4$, gave the cyclo-octanone (**18**) (35 mg, 0.18 mmol, 23%) after column chromatography (5 × 2 cm, 20% light petroleum in Et_2O) and distillation, b.p. 100 °C (bath)/0.2 mmHg; $\nu_{max.}$ 3 440s, 1 690s, and 1 065s cm^{-1}; δ_H (400 MHz) 3.94 (1 H, m), 3.67 (4 H, m), 2.79 (1 H, ddd, *J* 16, *J'* 3, *J''* 1.5), 2.543 (1 H, dd, *J* 15, *J'* 16), 2.489 (1 H, d, *J* 11), 2.10 (1 H, s, OH), 1.970 (1 H, d, *J* 11), 1.14—1.73 (6 H, m), and 0.933 (6 H, s) (Found: M^+, 214.156 67. $C_{12}H_{22}O_3$ requires *M*, 214.156 885).

1-*Acetyl*-2-(4-*oxobutyl*)*benzene* (**59**).—Ozonolysis of the alkene (**58**)[27] (2.66 g, 16.5 mmol), in MeOH (50 cm^3) at −78 °C with a Me_2S work-up[28] gave the aldehyde (**59**) (1.56 g, 8.24 mmol, 50%) after column chromatography (5 × 3.5 cm, CH_2Cl_2), $\nu_{max.}$ 1 725s and 1 685s cm^{-1}; δ_H 9.80 (1 H, t, *J* 1), 7.74 (1 H, m), 7.36 (3 H, m), 2.91 (2 H, dt, *J* 1, *J'* 7), 2.68 (2 H, m), 2.6 (2 H, m), and 1.9 (2 H, m) (Found: M^+, 190.099 47. $C_{12}H_{14}O_2$ requires *M*, 190.900 373).

2-[3-(2-*Acetylphenyl*)*propyl*]-1,3-*dioxolane* (**60**).—Reaction of the keto aldehyde (**59**) (500 mg, 2.63 mmol) with ethylene glycol (167 mg, 2.7 mmol) in CH_2Cl_2 (5 cm^3) containing *p*-TsOH (5 mg) and anhydrous Na_2SO_4 (1 g) gave the dioxolane (**60**) (380 mg, 2.0 mmol, 75%) after column chromatography (4 × 2.5 cm, CH_2Cl_2) and distillation, b.p. 120 °C (bath)/0.4 mmHg; $\nu_{max.}$ 1 685s and 1 160s cm^{-1}; δ_H 7.6 (1 H, m), 7.2 (3 H, m), 4.8 (1 H, m), 3.8 (4 H, m), 2.9 (2 H, m), 2.53 (3 H, s), and 1.7 (4 H, m) (Found: M^+, 234.125 66. $C_{14}H_{18}O_3$ requires *M*, 234.125 586).

8-(2-*Hydroxyethoxy*)-7,8,9,10-*tetrahydrobenzocyclo-octen*-5(6H)-*one* (**4**).—Reaction of the enol silane (**1**) prepared from the ketone (**60**) (678 mg, 2.9 mmol) with $TiCl_4$ in the usual way gave the cyclo-octanone (**4**) (366 mg, 1.56 mmol, 53%) after column chromatography (6 × 2.5 cm, 10% Et_2O in CH_2Cl_2) and distillation, b.p. 150 °C (bath)/0.2 mmHg; $\nu_{max.}$ 1 665s and 1 110s cm^{-1}; δ_H 7.96 (1 H, m), 7.1—7.6 (3 H, m), 3.8 (1 H, m), 3.67 (4 H, m), 3.291 (2 H, d, *J* 6), 3.168 (2 H, dd, *J* 12, *J'* 6), 2.882 (1 H, s, OH), 1.5—2.1 (4 H, m) (Found: M^+, 234.125 52. $C_{14}H_{18}O_3$ requires *M*, 234.125 586).

1-*Acetyl*-2-(4,4-*dimethoxybutyl*)*benzene* (**61**).—The keto aldehyde (**59**) (678 mg, 3.57 mmol) was converted to the acetal (**61**) (764 mg, 3.23 mmol, 90%) by the method of Gemal and Luche,[23] $\nu_{max.}$ 1 685s and 1 070s cm^{-1}; δ_H 7.63 (1 H, m), 7.3 (3 H, m), 4.4 (1 H, m), 3.29 (6 H, s), 2.9 (2 H, m), 2.54 (3 H, s), and 1.64 (4 H, m).

7-*Methoxy*-7,8,9,10-*tetrahydrobenzocyclo-octen*-5(6*H*)-*one* (**22**).—Reaction of the enol silane (**13**) prepared from the keto acetal (**61**) (764 mg, 3.23 mmol) with $TiCl_4$ in the usual way gave the cyclo-octanone (**22**) (282 mg, 1.38 mmol, 38%) after column chromatography (10 × 2.5 cm, CH_2Cl_2), $\nu_{max.}$ 1 665s and 1 090s cm^{-1}; δ_H 8.0 (1 H, m), 7.4 (3 H, m), 3.7 (1 H, m), 3.38 (3 H, s), 3.27 (2 H, dd, *J* 5.5, *J'* 1.5), 3.2 (2 H, m), 2.1 (1 H, m), and 1.65 (3 H, m); (Found: M^+, 204.115 11. $C_{13}H_{16}O_2$ requires *M*, 204.115 023).

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