Iron(III) mediated transformations of cyclopropyltrimethylsilyl ethers. Part 1. Free radical tandem ring expansion–cyclisation reactions for the rapid construction of [*n*.3.0] bicyclic ring systems

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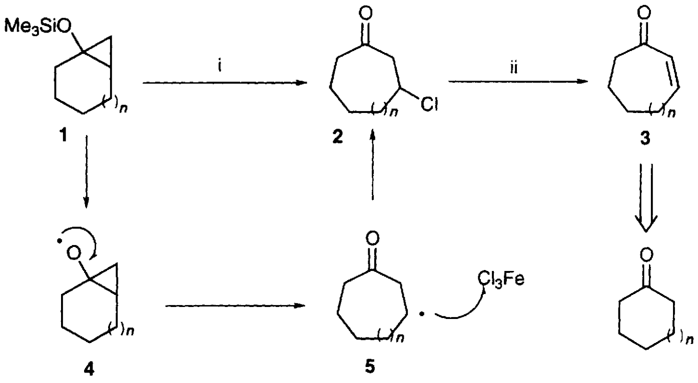
Treatment of a number of [*n*.1.0] cyclopropyl trimethylsilyl ethers with anhydrous ferric chloride in dry dimethylformamide leads to diastereoisomerically pure [*n*.3.0] bicyclic chloro ketones by a novel tandem ring expansion–cyclisation sequence. The reaction is thought to proceed by a mechanism involving the intermediacy of a cyclopropyl alkoxy radical.

Recently we reported[1,2] a novel method for the synthesis of [*n*.3.0] bicyclic ketones based on the ferric chloride-induced ring expansion of cyclopropyl trimethylsilyl ethers. In this paper we would like to delineate our full experimental procedures for the preparation of these important classes of ring systems.

In 1976 Saegusa[3] *et al.* reported that treatment of cyclopropyl trimethylsilyl ethers (*e.g.* **1**) with anhydrous ferric chloride in dimethylformamide (DMF) gave rise to the β-chloro ketone **2** which upon treatment with sodium acetate in methanol yielded the corresponding enone **3**. Although the mechanism is not fully understood it was thought to proceed by formation of the cyclopropyl alkoxy radical **4** followed by β-scission to the ring expanded carbocyclic radical **5** and chlorine abstraction to yield the β-chloro ketone **2**. The overall process provides an elegant and convenient three-step procedure for the conversion of cyclic ketones into the homologous one carbon ring-expanded cyclic enones (Scheme 1).



Scheme 1 *Reagents and conditions:* i, FeCl$_3$ (2.2 equiv.), DMF 0 °C; ii, NaOAc, MeOH

It occurred to us that if this reaction is indeed a free-radical process then it may be possible to trap out the intermediate ring-expanded carbocyclic radical **5** by 5-*exo* cyclisation onto a suitable acceptor. We reasoned that treatment of the cyclopropyl silyl ether **6**, containing a suitably attached but-3-enyl moiety, with ferric chloride would yield the ring-expanded carbocyclic radical **7**, which should undergo a rapid 5-*exo* cyclisation followed by chlorine abstraction to yield the bicyclic chloro ketone **8** (Scheme 2).

Results and discussion

Synthesis of 10-(chloromethyl)bicyclo[5.3.0]decan-3-one ring system

Our initial investigations began with the synthesis of the cyclopropyl trimethylsilyl ether **6** which utilised the methodology developed by Matsuzawa[4] *et al.* for the conjugate addition of Grignard reagents to enones in the presence of trimethylsilyl chloride (TMSCl). Thus, we found that addition of but-3-enylmagnesium bromide to cyclohex-2-enone gave the silyl enol ether **9** in 88% yield. Cyclopropanation[3] of **9** with Et$_2$Zn–CH$_2$I$_2$ yielded the cyclopropyl trimethylsilyl ether **6** as a single diastereoisomer (85%). The high chemoselectivity observed in the conversion of **9** into **6** can be attributed to the faster rate of reaction of the electrophilic zinc carbenoid with the more electron-rich enol ether double bond and, in fact, even with a two-fold excess of reagent monocyclopropanation was only ever observed. Although we were unable to assign the relative stereochemistry of **6** on the basis of NMR results, we believe that the *trans* isomer as shown is formed by axial attack of the carbenoid on the cyclohexene ring. Eventually, after much experimentation, we were delighted to find that treatment of **6** with 2.2 equiv. of anhydrous ferric chloride in dry DMF yielded the *trans* fused bicyclic chloro ketone **10** as a single diastereoisomer in 64% yield (Scheme 3). It was found that the time of addition of the ferric chloride was crucial and optimised yields were obtained with addition times of *ca.* 40 min. If the addition of ferric chloride was too rapid then substantial amounts of uncyclised β-chloro ketone **11** were obtained. This is presumably formed because rapid addition leads to higher concentrations of ferric chloride which would effectively scavenge the carbocyclic radical **7** before 5-*exo* cyclisation could take place. On the other hand if the rate of addition was too slow (2–12 h) then complex reaction mixtures resulted with only trace amounts of **10** formed.

Owing to the complexity of the ^{1}H NMR spectrum of **10** it was impossible to assign the relative stereochemistry of the three chiral centres by NOE experiments and so a crystalline derivative of **10** was synthesised for X-ray studies. This was readily achieved by conversion of **10** into the sulfide **12** with the potassium salt of benzenethiol (80%) followed by oxidation of this[5] (93%) with Oxone® to give the highly crystalline sulfone **13**. X-Ray analysis of a single crystal of **13** thus elucidated the stereochemical outcome of the ring expansion–cyclisation sequence and the molecular structure is as shown in Scheme 4. The *trans* fused ring junction can be explained by considering that the intermediate carbocyclic radical can exist

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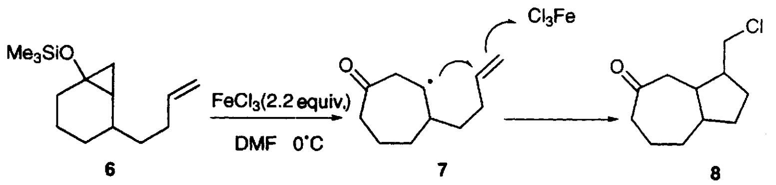
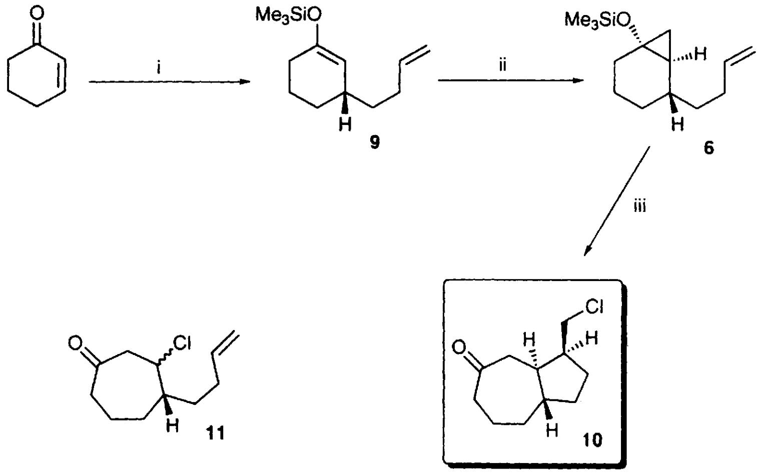


Scheme 2



Scheme 3 *Reagents and conditions:* i, But-3-enylmagnesium bromide, 10% CuI, hexamethylphosphoramide (HMPA), THF −78 °C, then cyclohex-2-enone, Me_3SiCl; ii, Et_2Zn, CH_2I_2, Et_2O; iii, $FeCl_3$ (2.2 equiv.), DMF 0 °C

in two possible chair-like conformations **14** and **15**. In conformation **14** the butenyl side chain is axial and would be disfavoured, whereas in **15** the side chain is equatorial and it is this lower energy conformer that would be expected to lead to the stereochemistry observed.

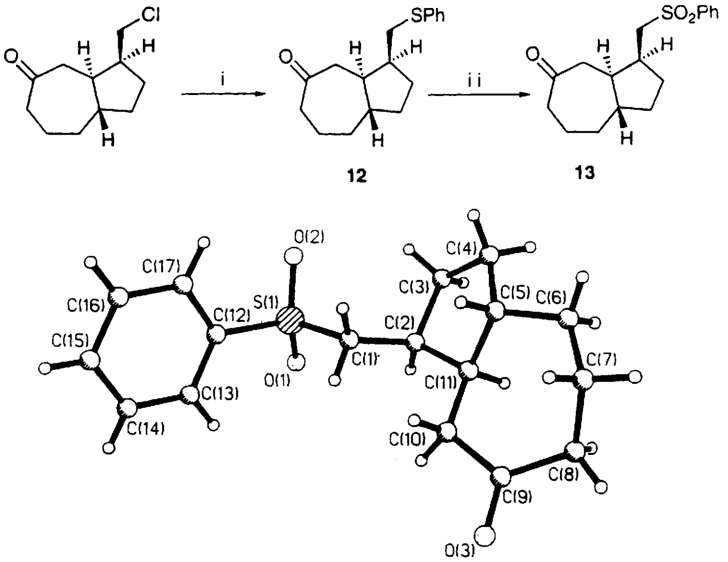
Synthesis of the 9-(chloromethyl)bicyclo[4.3.0]nonan-3-one ring system

Conjugate addition of butenylmagnesium bromide to cyclopent-2-enone gave the corresponding enol ether **16** (92%) which after cyclopropanation with $Et_2Zn–CH_2I_2$ gave **17** in excellent yield (91%). It is interesting to compare the rates of cyclopropanation of both **9** and **16** for which we used commercially available diethylzinc solution (1 mol dm^{-3} in hexanes). The six-membered enol ether **9** required a period overnight under reflux to go to completion, whereas the five-membered enol ether **16** generally went to completion within 2 h. This higher reactivity towards the zinc carbenoid can probably be attributed to the greater inherent strain present in the five-membered enol ether. It should be noted that although these cyclopropanations are very efficient, they are *extremely sensitive* to air/moisture and even brief exposure of the reaction contents to the atmosphere results in termination of the cyclopropanation sequence. Furthermore, we also found that use of 2 equiv. of *neat* diethylzinc results in an instantaneous, and exothermic, cyclopropanation of **16** from which **17** could be isolated in an optimised 87% yield. It should be noted, however, that this beneficial reaction time has to be weighed up against the extreme pyrophoric nature of neat diethylzinc and its attendant handling problems (see Experimental section). Ring-expansion cyclisation was initially carried out at 0 °C as before, however, this gave very poor yields of cyclised product (~10%), and the bulk of the starting material was consumed to give unidentified, polar material. It was felt that the more strained and hence more reactive cyclopropane **17** was unstable in $DMF–FeCl_3$ at this temperature. A repeat of the reaction at −40 °C allowed the bicyclic chloro ketone **18** to be isolated as a single diastereoisomer in an optimised yield of 51%. The stereochemistry of **18** is based on comparison[6] to the major products obtained from the cyclisation of the hexenyl radicals **19** and **20** from which the *cis* fused *endo* isomers predominated in both cases (Scheme 5).

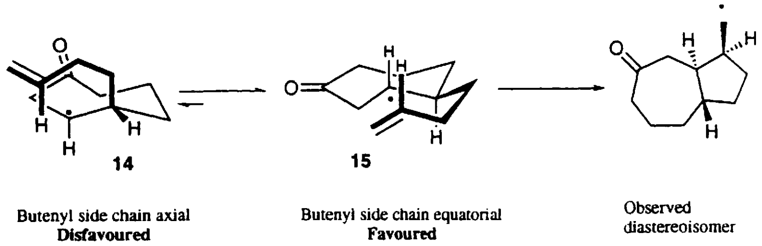
In an attempt to synthesise a crystalline derivative of **18** we uncovered a rather interesting result regarding acetal formation. Treatment of **18** with the potassium salt of benzenethiol in ethanol gave not the expected keto sulfide **21** but the diethyl acetal **22** in 47% yield. Use of methanol as solvent gave the corresponding dimethyl acetal although this was difficult to isolate pure. Formation of acetals under basic conditions has been observed before[7] but only with special cases such as very electron deficient or strained carbonyl groups. This does not seem to be a general procedure for the formation of acetals as we found that there was no reaction of either cyclohexanone or the methyl ketone **23** under these conditions. We therefore postulated that this reactivity towards acetal formation under basic conditions may be due to the initial formation of the desired sulfide **21**, in which the close proximity of the sulfur atom to the carbonyl carbon in some way facilitates the formation of **22**. Treatment of the chloro ketone[8] **24** under identical conditions, however, gave only the normal substitution product **25**, albeit in rather poor yield (21%). We can only assume, therefore, that this peculiar observation is an anomaly restricted to the bicyclic chloro ketone **18**, rather than a general reaction of halogeno ketones with similar atom–atom connectivities as shown for **24** (Scheme 6).

Synthesis of the 11-(chloromethyl)bicyclo[6.3.0]undecan-3-one ring system

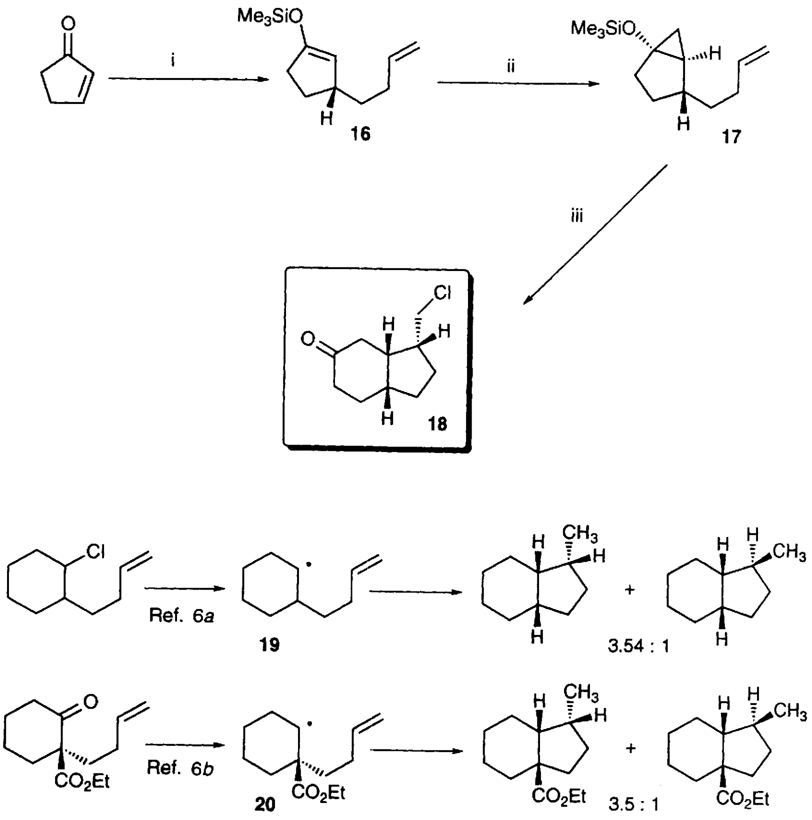
We next turned our attention to the 8,5-ring system by subjecting cycloheptenone to conjugate addition with butenylmagnesium bromide, which yielded the enol ether **26** in 92% yield. Cyclopropanation of **26** gave the corresponding cyclopropyl ether **27** in 87% yield as a single diastereoisomer,



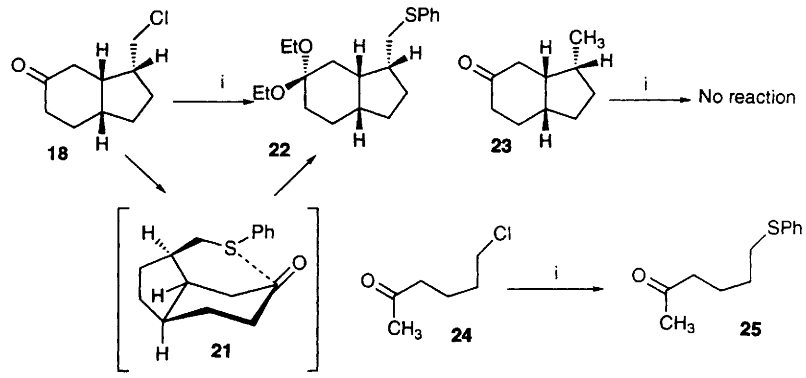
Molecular structure of **13**



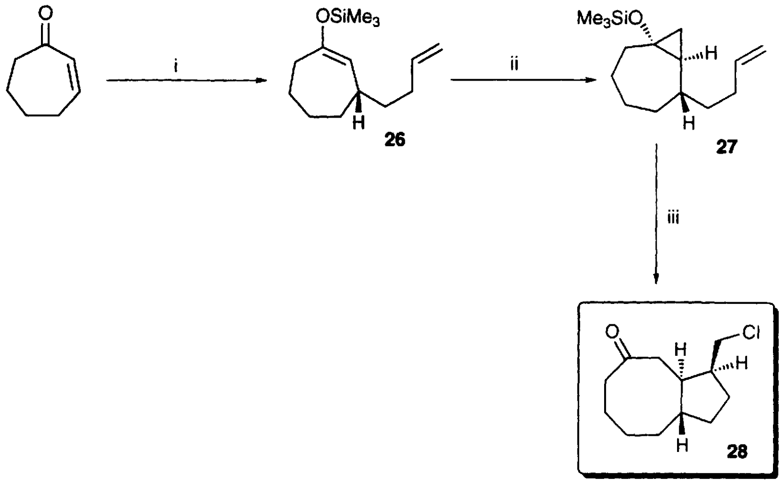
Scheme 4 *Reagents and conditions:* i, PhSH, Bu^{t}OK, MeOH; ii, Oxone®, MeOH, H_2O



Scheme 5 *Reagents and conditions:* i, But-3-enylmagnesium bromide, 10% CuI, HMPA, THF −78 °C, then cyclopent-2-enone, Me_3SiCl; ii, Et_2Zn, CH_2I_2, Et_2O; iii, $FeCl_3$ (2.2 equiv.), DMF −40 °C



Scheme 6 *Reagents and conditions:* i, PhSH, Bu^{t}OK, EtOH

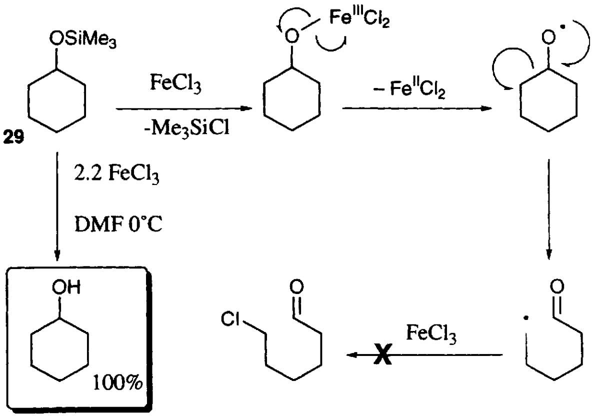


Scheme 7 *Reagents and conditions:* i, But-3-enylmagnesium bromide, 10% CuI, HMPA, THF −78 °C, then cyclohept-2-enone, Me$_3$SiCl; ii, Et$_2$Zn, CH$_2$I$_2$, Et$_2$O; iii, FeCl$_3$ (2.2 equiv.), DMF 0 °C

although the reaction times were similar to that observed for the six-membered enol ether. Ring expansion–cyclisation proceeded without event to give the 8,5- bicyclic chloro ketone **28** isolated as a single diastereoisomer in 48% yield. Although the relative stereochemistry of **28** is yet to be proved by crystallography, independent studies[9] published after our initial communication of this work, involving related ring expansions with Mn^{III} salts, corroborate the stereochemistry shown in Scheme 7.

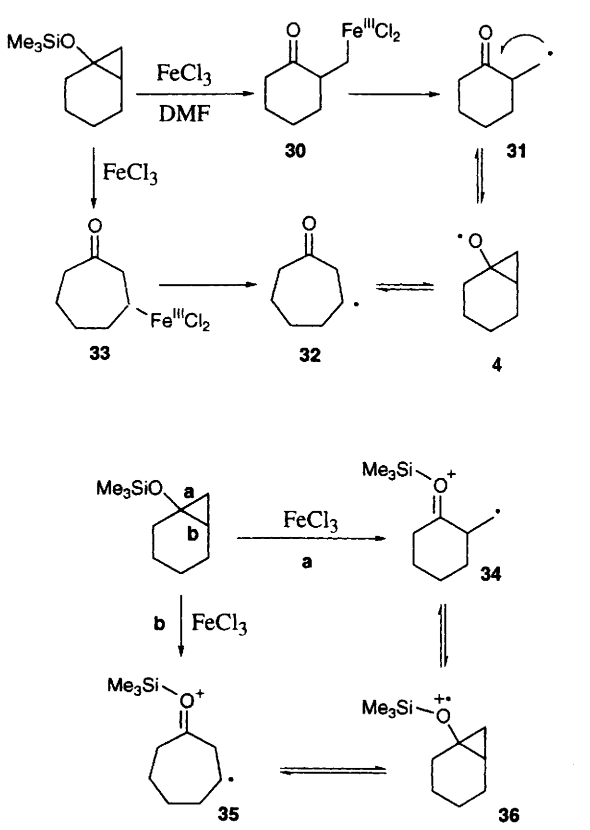
Mechanism

Although all the results we had obtained thus far certainly supported a free-radical mechanism, we were interested to see whether a cyclopropyl alkoxy radical (*e.g.* **4**) was actually involved and exactly how and at which point it was formed. If **4** was formed directly by cleavage of the oxygen–silicon bond then it would not be unreasonable to assume that treatment of any silyl ether with ferric chloride would lead to alkoxy radical formation. With this in mind we treated the silyl ether **29** with 2.2 equiv. of ferric chloride and isolated only the desilylated cyclohexanol rather than any products resulting from fragmentation of an alkoxy radical as shown in Scheme 8.



Scheme 8

This would seem to indicate that the cyclopropane ring is an essential part of the mechanistic picture and that prior ring opening is required to initiate a free-radical process. Two possible mechanisms are outlined in Scheme 9. Firstly, Lewis acid-catalysed ring opening of the cyclopropane gives the iron(III) homoenolate **30**; this is in analogy with the known TiCl$_4$ and SnCl$_4$ ring opening of cyclopropyl ethers to give the titanium and tin homoenolates respectively.[10] Homolytic fission of the iron–carbon bond (reduction of Fe^{III} to Fe^{II}) generates the radical **31** which undergoes rearrangement to the carbocyclic radical **32** *via* the cyclopropyl alkoxy radical **4**, 5-*exo* radical cyclisation followed by chlorine abstraction in the butenyl substituted cases then gives the product **2**. This type rearrangement has been extensively studied by Beckwith and Dowd.[11] It could be envisioned that a ring-expanded iron homoenolate **33** could lead directly to **32**, however, this is less likely as Lewis acids tend to give metal homoenolates by ring cleavage rather than expansion.[10] The second possibility



Scheme 9

involves single electron transfer from either cyclopropane bond **a** or **b** to give the radical-cations **34** and **35**, which could be in equilibrium with each other through the cyclopropyl radical cation **36** or the desilylated alkoxy radical **4**.

In conclusion, the above methodology allows diastereoselective access to three important [*n*.3.0] bicyclic ring systems from commercially available starting materials in just three steps and as such should prove useful in the synthesis of natural products containing such ring systems.

Experimental

All compounds are racemic mixtures, named according to the relative stereochemical assignments drawn in the text. Bps refer to Kugelrohr oven temperature during distillation. All manipulations involving anhydrous ferric chloride (Aldrich) were carried out in a glove bag under an atmosphere of argon or nitrogen. DMF was dried by distillation from calcium hydride immediately before use. IR spectra were run neat as thin films on a Perkin-Elmer 1720 X FT spectrometer. ^{1}H and ^{13}C spectra were recorded on a Bruker AC 300 or a JEOL EX 270 FT spectrometer in either deuteriochloroform or deuteriobenzene. Chemical shifts are referenced to tetramethylsilane, or in the case of any of the trimethylsilyl compounds to the residual $CHCl_3$ or C_6H_6 signals and *J* values are in Hz. Mass spectra were recorded at low resolution on a Finnigan 4500 instrument and at high resolution on a Kratos Concept 1-S instrument. Mass spectra were recorded under electron-impact (EI) conditions, or chemical ionisation (CI) conditions using ammonia. Light petroleum refers to the fraction boiling at 40–60 °C. TLC was performed using Camlab Polygram® SIL G/UV$_{254}$ plastic plates, visualised by the combination of a UV lamp and subsequent staining with acidified aqueous potassium permanganate followed by heating. Flash chromatography was performed using Merck silica gel 60 (particle sizes 40–60 μm).

(3*S)-(But-3-enyl)-1-trimethylsilyloxycyclohex-1-ene 9**

To a stirred suspension of magnesium metal (0.61 g, 25.0 mmol; activated by heating with a crystal of I_2, under Ar) in dry THF (40 cm^3), under an Ar atmosphere, was added 4-bromobut-1-ene (2.54 cm^3, 25.0 mmol). After the initial exotherm had subsided the reaction mixture was stirred for 1 h after which HMPA (9 cm^3) was added to it; the mixture was then cooled to −78 °C. Copper iodide (0.39 g, 2.05 mmol) was added to the cooled mixture which was then stirred for 10 min before a mixture of cyclohex-2-enone (2.0 g, 20.8 mmol) and TMSCl (6.2 cm^3, 48.85 mmol) in THF (20 cm^3) were added dropwise to it over 10 min. The resulting white suspension was stirred for 1 h at −78 °C, before the addition of Et_3N (5 cm^3). After being allowed to warm to room temperature, the resulting suspension was poured onto light petroleum (250 cm^3) and the mixture washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to give a clear yellow oil. Kugelrohr distillation of this (130–140 °C at 20 mm Hg) gave a clear yellow liquid (4.1 g, 88%); ν_{max}/cm^{-1} 2920, 1665 and 1640; δ_H(300 MHz; C_6D_6) 0.17 (9 H, m, $SiMe_3$), 0.79–1.8 (2 H, m), 1.9–1.65 (4 H, m), 1.96–2.19 (5 H, m), 4.88 (1 H, br s, 2-H), 4.93–5.05 (2 H, m, 4′-H) and 5.66–5.73 (1 H, m, 3′-H); δ_C(75.47 MHz) 0.44 ($SiMe_3$), 22.04 (CH_2), 29.06 (CH_2), 30.48 (CH_2), 31.67 (CH_2), 34.42 (CH), 36.72 (CH_2), 108.68 (C-2), 114.47 (C-4′), 139.19 (C-3′) and 151.02 (C-1) {Found: *m*/*z* (NH_3, CI), 225.1677, [M + 1]$^+$. $C_{13}H_{25}OSi$ requires 225.1675}.

(1*R,5*S**,6*S**)-5-(But-3′-enyl)-1-trimethylsiloxybicyclo[4.1.0]-heptane 6**

Compound **9** (3.85 g, 17.2 mmol) was weighed into dry apparatus under Ar before the addition of dry diethyl ether (30 cm^3), diethylzinc (1 mol dm^{-3} solution in hexane; 20.6 cm^3, 20.6 mmol) and diiodomethane (1.66 cm^3, 20.6 mmol). The solution was refluxed for 18 h after which a further 0.3 equiv. of both diethylzinc and diiodomethane were added and the reaction mixture was heated at reflux for a further 6 h. After the resulting cloudy solution had been allowed to cool and pyridine (3 cm^3) had been slowly added dropwise to it with stirring, the resulting precipitate was washed into a conical flask with light petroleum (250 cm^3). The resulting white suspension was filtered, and the filtrate evaporated to give a yellow liquid. Kugelrohr distillation of this (130–140 °C at 20 mm Hg) gave a clear, colourless liquid (3.46 g, 85%); ν_{max}/cm^{-1} 2920 and 1640; δ_H(300 MHz; $CDCl_3$) 0.13 (9 H, s, $SiMe_3$), 0.29 (1 H, t, *endo*-7-H), 0.75–0.97 (4 H, m), 1.15–1.39 (2 H, m), 1.4–1.68 (4 H, m), 1.7–1.89 (1 H, m), 2.05–2.24 (2 H, m) 4.85–5.09 (2 H, m, CH_2-4′) and 5.82 (1 H, m, CH_2-3′); δ_C(75.47 MHz) 1.40 ($SiMe_3$), 18.88 (CH_2), 21.26 (CH_2), 24.66 CH), 29.89 (CH_2), 31.52 (CH_2), 31.95 (CH_2), 37.49 (CH_2), 37.56 (CH), 57.18 (quat.), 114.25 (C-4′) and 138.89 (C-3′) {Found: *m*/*z* (NH_3, CI), 239.1824, [M + 1]$^+$. $C_{14}H_{27}OSi$ requires 239.1831}.

(1*R,7*S**,10*S**)-10-Chloromethylbicyclo[5.3.0]decan-3-one 10**

To a stirred solution of the cyclopropane **6** (0.476 g, 2 mmol) in dry DMF (40 cm^3), under argon at 0 °C, was added dropwise over 40 min (from a pressure equalised dropping funnel) a solution of anhydrous ferric chloride (0.714 g, 4.4 mmol) in dry DMF (40 cm^3). The resulting yellow–brown solution was stirred at 0 °C for a further 1 h after which it was poured onto water (500 cm^3) and extracted with ethyl acetate (3 × 200 cm^3). The organic extracts were washed with water (2 × 200 cm^3), dried and evaporated to give a pale brown oil. Flash chromatography of this (10% diethyl ether–light petroleum) gave the product as a clear oil (0.258 g, 64%); ν_{max}/cm^{-1} 2925, 1700 and 910; δ_H(300 MHz; $CDCl_3$) 1.08–1.38 (3 H, m), 1.42–1.69 (3 H, m), 1.75–2.09 (5 H, m), 2.30–2.68 (4 H, m), 3.35 (1 H, dd, J_{vic} 8.44, J_{gem} 10.77, CH_2Cl) and 3.52 (1 H, dd, J_{vic} 5.43, J_{gem} 10.85, CH_2Cl); δ_C(75.47 MHz, $CDCl_3$) 24.76 (CH_2), 28.89

(CH_2), 32.41 (CH_2), 35.70 (CH_2), 43.25 (CH), 43.62 (CH_2), 44.13 (CH_2), 45.08 (CH), 46.37 (CH_2), 47.65 (CH), 213.81 (C=O) {Found: *m*/*z* (NH_3, CI) 218.1312 $[M + NH_4]^+$. $C_{11}H_{21}ClNO$ requires 218.1312}.

(1*R**,7*S**,10*S**)-10-(Phenylsulfanylmethyl)bicyclo[5.3.0]decan-3-one 12

To a stirred solution of compound **10** (0.18 g, 0.9 mmol) in ethanol (10 cm^3) was added benzenethiol (0.11 cm^3, 0.99 mmol) and potassium *tert*-butoxide (0.11 g, 0.99 mmol). The reaction mixture was heated at reflux for 24 h under Ar before being poured onto water (150 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The organic extracts were washed with 1 mol dm^{-3} aqueous NaOH (100 cm^3), and water (100 cm^3), dried and evaporated to give a yellow liquid. Flash chromatography (15% diethyl ether–light petroleum) gave the product as a clear, viscous oil (0.197 g, 80%); ν_{max}/cm^{-1} 2985, 1698 and 1601 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 1.12–1.35 (2 H, m), 1.46–1.72 (3 H, m), 1.75–2.13 (6 H, m), 2.15–2.34 (1 H, m), 2.36–2.7 (4 H, m), 2.96 (1 H, dd, J_{vic} 4.66, J_{gem} 12.16, CH_2S), 7.07–7.36 (5 H, m Ph); δ_C(75.47 MHz) 24.84 (CH_2), 30.00 (CH_2), 32.23 (CH_2), 35.28 (CH_2), 35.76 (CH_2), 42.25 (CH), 43.68 (CH_2), 43.80 (CH), 44.75 (CH_2), 47.17 (CH), 125.82 (CH), 128.81 (CH), 128.96 (CH), 136.57 (quat.) and 213.96 (C=O) {Found: *m*/*z* (NH_3, CI) 292.1730, $[M + NH_4]^+$. $C_{17}H_{26}NOS$ requires 292.1735}.

(1*R**,7*S**,10*S**)-10-(Phenylsulfonylmethyl)bicyclo[5.3.0]decan-3-one 13

To a stirred solution of the sulfide **12** (0.1 g, 0.36 mmol) in MeOH (5 cm^3) was added a solution of Oxone® (0.68 g, 1.1 mmol) in water (5 cm^3). The resulting suspension was stirred for 2.5 h after which it was poured onto water (100 cm^3) and extracted with chloroform (100 cm^3). The chloroform extracts were dried and the solvent evaporated to give a clear oil which upon trituration with diethyl ether gave the pure sulfone as white crystals (0.102 g, 93%); mp 136.5–137 °C; ν_{max}/cm^{-1} 2957, 1700 and 1599; δ_H(300 MHz; $CDCl_3$) 1.12–1.31 (2 H, m), 1.31–1.55 (2 H, m), 1.56–1.71 (1 H, m), 1.78–2.24 (6 H, m), 2.35–2.6 (4 H, m), 2.91 (1 H, dd, J_{vic} 9.81, J_{gem} 13.88, CH_2SO_2Ph), 3.05 (1 H, dd, J_{vic} 3.88, J_{gem} 13.84, CH_2SO_2Ph), 7.4–7.65 (m, 3 H) and 7.85, (d, 2 H); δ_C(75.47 MHz) 25.02 (CH_2), 30.47 (CH_2), 32.27 (CH_2), 35.47 (CH_2), 37.45 (CH), 43.37 (CH), 43.51 (CH_2), 45.05 (CH_2), 47.38 (CH), 57.03 (CH_2), 127.82 (CH), 129.34 (CH), 133.77 (CH), 139.68 (quat.) and 213.03 (C=O) {Found: *m*/*z* (NH_3, CI) 307.1343, $[M + H]^+$. $C_{17}H_{23}SO_3$ requires 307.1368}.

Crystal data for compound 13. $C_{17}H_{22}O_3S$, *M* 306.4, colourless, regular, monoclinic crystal, dimensions 0.4 × 0.3 × 0.3 mm, space group $P2_1/n$, $a = 5.633(2)$, $b = 19.942(5)$, $c = 13.879(5)$ Å, $\beta = 94.22(2)°$, $Z = 4$, $V = 1554.9(8)$ Å^3, $D_c = 1.309$ g cm^{-3}.

Data collection and processing. Siemens R3m/V diffractometer, scan type 2θ–θ, 2θ range = 3.0–50.0 °, ω scan speed = 3.0 – 15.0 ° min^{-1}, scan range = 0.60 ° plus Kα-separation, graphite monochromated Mo-Kα radiation (λ = 0.710 73 Å), 6106 reflections collected ($-6 \leqslant h \leqslant 2$, $-23 \leqslant k \leqslant 23$, $-16 \leqslant l \leqslant 16$), 2758 independent reflections (R_{int} = 1.86%), 2133 observed reflections [$F > 4.0\,\sigma(F)$].

Structure analysis and refinement. Structure solved by direct methods using the SHELXTL PLUS (VMS) program and refined using the full matrix least squares method, using a $w^{-1} = \sigma^2(F) + 0.0005F^2$ weighting scheme. The final *R* and R_w indices were 4.32 and 5.19%, respectively.

(3*R**)-(But-3-enyl)-1-trimethylsiloxycyclopent-1-ene 16

To a stirred suspension of magnesium metal (0.61 g, 36.59 mmol, activated by heating with a crystal of I_2, under Ar) in dry THF (40 cm^3), under an Ar atmosphere, was added 4-bromobut-1-ene (2.54 cm^3, 29.27 mmol). After the initial exotherm had subsided the reaction mixture was stirred for 1 h after which HMPA (10 cm^3, 58.53 mmol) was added to it; the mixture was then cooled to −78 °C. Copper iodide (0.46 g, 2.44 mmol) was added to the cooled mixture which was then stirred for 10 min before a mixture of cyclopent-2-enone (2.0 g, 24.39 mmol) and TMSCl (7.43 cm^3, 58.52 mmol) in THF (20 cm^3) were added dropwise to it over 10 min. The resulting white suspension was stirred for 1 h, before the addition of Et_3N (5 cm^3). After being allowed to warm to room temperature, the resulting suspension was poured onto light petroleum (250 cm^3), washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to give a clear yellow oil. Kugelrohr distillation of this (110–120 °C at 15 mm Hg) gave a clear yellow liquid (4.7 g, 92%); ν_{max}/cm^{-1} 2955 and 1643 (C=C); δ_H(300 MHz; C_6D_6) 0.15 (9 H, s, $SiMe_3$), 1.3–1.5 (3 H, m), 1.9–2.1 (3 H, m) 2.26 (2 H, m), 2.58 (1 H, m, 3-H), 4.65 (1 H, br d, 2-H), 4.9–5.1 (2 H, m, CH_2-4′) and 5.75 (1 H, m, 3′-H); δ_C(75.47 MHz) 0.03 ($SiMe_3$), 28.39 (CH_2), 32.26 (CH_2), 33.64 (CH_2), 37.01 (CH_2), 41.87 (CH-3), 106.39 (C-4′), 114.36 (C-3′), 139.25 (C-2) and 155.28 (C-1) [Found: *m*/*z* (EI) 210.1443. $C_{12}H_{22}OSi$ requires 210.1440].

(1*R**,4*R**,5*S**)-4-(But-3′-enyl)-1-trimethylsiloxybicyclo[3.1.0]hexane 17

(*a*) Compound **16** (3.0 g, 14.29 mmol) was weighed into a dry apparatus under Ar before the addition of dry diethyl ether (40 cm^3), diethylzinc (1 mol dm^{-3} solution in hexane; 17.1 cm^3, 17.15 mmol) and diiodomethane (1.38 cm^3, 17.15 mmol). The solution was heated at reflux for 2 h to give a cloudy solution which was allowed to cool and then quenched by the dropwise addition of pyridine (3 cm^3). The resulting precipitate was washed into a conical flask with light petroleum (250 cm^3) and the resulting white suspension was filtered, and the filtrate evaporated to give a yellow liquid. Kugelrohr distillation of this (bp 120–130 °C at 15 mm Hg) gave a clear, colourless liquid (2.9 g, 91%); ν_{max}/cm^{-1} 2930 and 1630; δ_H(300 MHz; C_6D_6) 0.12 (9 H, s, $SiMe_3$), 0.52 (1 H, t, *endo* 6-H), 0.76 (1 H, m, *exo* 6-H), 1.18–1.49 (5 H, m), 1.67 (1 H, m), 1.82–2.10 (4 H, m), 4.89–5.01 (2 H, m, CH_2-4′) and 5.79 (1 H, m, 3′-H); δ_C(75.47 MHz) 9.37 ($SiMe_3$), 24.23 (CH_2), 35.27 (CH_2), 36.92 (CH), 40.18 (CH_2), 40.58 (CH_2), 43.19 (CH_2), 47.58 (CH), 73.09 (C-1), 122.66 (C-4′) and 147.15 (C-3′) [Found: *m*/*z* (EI) 224.1596. $C_{13}H_{24}OSi$ requires *m*/*z* 224.1596].

(*b*) **CAUTION**: The following procedure uses neat diethyl zinc which is *extremely pyrophoric* and must be handled in an inert atmosphere at all times during transfer. For the quantities used in this experiment we found it convenient to use a 5 cm^3 disposable plastic syringe equipped with a stainless-steel luer lock containing a stopcock valve (Aldrich), thus sealing the contents from the atmosphere during transfer. Compound **16** (2.5 g, 11.9 mmol) was weighed into dry apparatus under Ar before the addition of dry diethyl ether (10 cm^3), neat diethylzinc (2.44 cm^3, 23.81 mmol) and diiodomethane (1.92 cm^3, 23.81 mmol). After the initial exothermic reaction had subsided, the reaction mixture was stirred for a further 10 min, after which pyridine (4 cm^3) was added to it to give a yellow slurry. This was extracted by leaching with light petroleum, and the extracts evaporated to give a yellow liquid. Kugelrohr distillation of this (bp 120–130 °C at 15 mm Hg) to give the product **17** as before as a clear colourless liquid (2.32 g, 87%).

(1*S**,6*R**,9*R**)-9-Chloromethylbicyclo[4.3.0]nonan-3-one 18

To a stirred solution of compound **17** (0.448 g, 2.0 mmol) in dry degassed DMF (40 cm^3), was added a solution of anhydrous ferric chloride (0.714g, 4.4 mmol) in DMF (20 cm^3) *via* a syringe pump over 30 min, under Ar at −40 °C. After being stirred for a further 1 h at −40 °C, the mixture was allowed to warm to room temperature when it was poured onto water (400 cm^3) and extracted with EtOAc (4 × 150 cm^3). The organic extracts were washed with water (2 × 100 cm^3), dried and evaporated to give the crude product as a yellow liquid. Flash chromatography (15% diethyl ether–light petroleum) gave the pure product as a clear liquid (0.19 g, 51%); ν_{max}/cm^{-1} 2951 and 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 1.40–1.53 (1 H, m), 1.7–2.5 (12 H, m), 3.35 (1 H, dd, J_{gem} 10.8, J_{vic} = 8.9, CH_2Cl) and 3.45 (1 H, dd, J_{gem} 10.8, J_{vic} 6.3, CH_2Cl); δ_C(75.47 MHz) 27.27 (CH_2), 27.32 (CH_2), 27.87 (CH_2), 36.94 (CH_2), 37.25 (CH_2) and 37.42 (CH), 41.53 (CH), 44.78 (CH_2Cl), 47.91 (CH) and 212.89 (C=O) {Found: *m*/*z* (NH_3, CI) 204.1147, $[M + NH_4]^+$. $C_{10}H_{19}ClNO$ requires 204.1155}.

(1*S**,6*R**,9*R**)-3,3-Diethoxy-9-(phenylsulfanylmethyl)bicyclo[4.3.0]nonane 22

To a stirred solution of compound **18** (0.18 g, 0.97 mmol) in ethanol (10 cm^3), was added benzenethiol (0.12 cm^3, 1.07 mmol) and potassium *tert*-butoxide (0.12 g, 1.07 mmol). The reaction mixture was heated at reflux for 24 h under Ar before being poured onto water (150 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The organic extracts were washed with 1 mol dm^{-3} aqueous NaOH (100 cm^3) and water (100 cm^3), dried and evaporated to give a brown oil. Flash chromatography of this (5% diethyl ether–light petroleum) gave the product as a clear, colourless oil (0.153 g, 47%); ν_{max}/cm^{-1} 2949 and 1481; δ_H(300 MHz; $CDCl_3$) 1.12–1.28 (6 H, 2 overlapping triplet, *J* 7.1, acetal CH_3), 1.4–2.3 (13 H, m), 2.89 (2 H, d, *J* 7.8, CH_2S), 3.4–3.58 (4 H, 2 overlapping quartet, *J* 7.1, acetal CH_2) and 7.1–7.3 (5 H, m, Ph); δ_C(75.47 MHz) 15.42 (acetal CH_3), 15.61 (acetal CH_3), 23.57 (CH_2), 25.36 (CH_2), 28.28 (CH_2), 28.48 (CH_2), 28.69 (CH_2), 35.21 (CH_2S), 38.15 (CH), 39.38 (CH), 42.98 (CH), 54.77 (acetal CH_2), 55.17, (acetal CH_2), 100.35 (C-3), 125.33 (aryl CH), 128.73 (2 × aryl CH) and 137.24 (aryl CS) {Found: *m*/*z* (NH_3, CI) 289.1639, $[M - EtO]^+$. $C_{18}H_{25}OS$ requires 289.1626}.

6-(Phenylsulfanylmethyl)hexan-2-one 25

To a stirred solution of 6-chlorohexan-2-one (100 mg, 8.44 × 10^{-4} mol) in methanol (4 cm^3) was added Bu^tOK (92 mg, 1.1 equiv.) and benzenethiol (0.083 cm^3, 1.1 equiv.) and the resulting solution was heated at reflux under N_2 for 18 h. Water (30 cm^3) was added to the cooled mixture which was then extracted with diethyl ether (3 × 20 cm^3). The combined extracts were then rinsed with 1 mol dm^{-3} aqueous NaOH (30 cm^3) and water (30 cm^3), dried and evaporated to give a pale brown oil. Flash chromatography of this (20% diethyl ether–light petroleum) gave the pure product (35 mg, 21%); ν_{max}/cm^{-1} 2934 and 1715 (C=O); δ_H(270 MHz; $CDCl_3$) 1.69 (4 H, m, CH_2-4, CH_2-5), 2.12 (3 H, s, CH_3-1), 2.44 (2 H, t, *J* 6.9, CH_2-3), 2.91 (2 H, t, *J* 6.9 Hz, CH_2-6) and 7.30 (5 H, m, Ph); δ_C(67.80 MHz) 22.8 (CH_2), 28.6 (CH_2), 29.9 (C-1), 33.4 (C-6), 43.1 (C-3), 125.9, 128.9, 129.1 (aryl CH), 136.5 (aryl C) and 208.5 (C=O) {Found: *m*/*z* (NH_3, CI) 209.1002, $[M + 1]^+$. $C_{12}H_{17}OS$ requires 209.1000}.

(3*S**)-(But-3′-enyl)-1-trimethylsiloxycyclohept-1-ene 26

With the same molar equivalents of reagents, cyclohept-2-enone (2 g, 18.8 mmol) was treated to the same procedure as described for the preparation of compound **9**, to give a pale yellow liquid after Kugelrohr distillation (150 °C at 15 mm Hg) (4.1 g, 92%); ν_{max}/cm^{-1} 2925 and 1655; δ_H(300 MHz; C_6D_6) 0.19 (9 H, s, $SiMe_3$), 1.28–1.47 (6 H, m), 1.54 (2 H, m, CH_2), 1.77 (1 H, m), 2.04–2.19 (3 H, m), 2.34 (1 H, m), 4.92 (1 H, d, *J* 4.6, 2-H), 4.96–5.09 (2 H, m, CH_2-4′) and 5.72–5.85 (1 H, m, 3′-H); δ_C(75.47 MHz) 0.08 ($SiMe_3$), 25.24 (CH_2), 30.00 (CH_2), 31.71 (CH_2), 34.15 (CH_2), 35.38 (CH_2), 35.77 (C-3), 36.81 (CH_2), 113.11 (C-2), 114.23 (C-4′), 138.80 (C-3′) and 155.09 (C-1) [Found: *m*/*z* (EI) 238.1748. $C_{14}H_{26}OSi$ requires 238.1752].

(1*R**,6*S**,7*S**)-6-(But-3′-enyl)-1-trimethylsiloxybicyclo[5.1.0]octane 27

With the same molar equivalents of reagents, compound **26** (2 g, 8.4 mmol) was treated to the same procedure as described for the preparation of compound **6**, except that after the initial 24 h period of reflux a further 0.4 equiv. of both diethylzinc and diiodomethane were added and the mixture refluxed for a further 2 h. Work-up as before and Kugelrohr distillation (120–130 °C at 15 mm Hg) yielded the product as a clear liquid (1.83 g, 87%); ν_{max}/cm^{-1} 2923 and 1641; δ_H(300 MHz; C_6D_6) 0.19 (9 H, s, $SiMe_3$), 0.27 (1 H, m, *endo* 8-H), 0.69–0.87 (2 H, m), 1.02–1.15 (2 H, m), 1.4–1.6 (6 H, m), 1.85–2.2 (4 H, m), 2.33 (1 H, m, CH-6), 5.05 (2 H, m, CH_2-4′) and 5.82 (1 H, m, CH-3′); δ_C(75.47 MHz) 1.53 ($SiMe_3$), 24.04 (CH_2), 25.41 (CH_2), 30.73 (CH), 31.47 (CH_2), 32.21 (CH_2), 36.47 (CH_2), 37.73 (CH_2), 38.30 (CH_2), 43.32 (CH), 59.59 (C-1), 114.33 (C-4′) and 139.47 (C-3′) [Found: *m*/*z* (EI) 252.1915. $C_{15}H_{28}OSi$ requires 252.1909].

(1*S**,8*S**,11*R**)-11-Chloromethylbicyclo[6.3.0]undeca-3-one 28

Compound **27** (0.504 g, 2 mmol) was treated with anhydrous ferric chloride (0.714 g, 4.4 mmol) by the same procedure as described for the preparation of compound **18**. Flash chromatography (20% diethyl ether–light petroleum) gave the product as a clear liquid. (0.21 g, 48%); ν_{max}/cm^{-1} 2931 and 1699 (C=O); δ_H(300 MHz; $CDCl_3$) 1.1–1.25 (2 H, m), 1.45–1.65 (5 H, m), 1.78–2.0 (6 H, m), 2.35–2.48 (3 H, m), 2.61 (1 H, br t), 3.36 (1 H, dd, J_{gem} 10.8, J_{vic} 7.7, CH_2Cl), 3.50 (1 H, dd, J_{gem} 10.8, J_{vic} 5.35, CH_2Cl); δ_C(75.47 MHz) 23.70 (CH_2), 26.60 (CH_2), 27.89 (CH_2), 29.92 (CH_2), 33.62 (CH_2), 42.14 (CH_2), 42.42 (CH), 43.13 (CH_2), 44.53 (CH), 47.32 (CH), 47.57 (CH_2Cl) and 214.19 (C=O) {Found: *m*/*z* (NH_3, CI) 232.1464, $[M + NH_4]^+$. $C_{12}H_{23}ClNO$ requires 232.1468}.

Acknowledgements

We thank the SERC for the provision of a studentship (D. F. T.), Dr A. Redhouse and Mr J. R. Thompson (University of Salford) for performing the X-ray crystallographic analysis, Dr M. Stuckey (University of Salford) for NMR spectra and Mrs R. Howard (University of Salford) for high resolution mass spectra.

References

1 K. I. Booker-Milburn, *Synlett*, 1992, 809.
2 K. I. Booker-Milburn and D. F. Thompson, *Synlett*, 1993, 592.
3 Y. Ito, S. Fujii, M. Nakatsuka, F. Kawamoto and T. Saegusa, *Org. Synth.*, Coll. Vol. 6, 1988, 327 and refs. cited therein.
4 S. W. Matsuzawa, Y. Horiguchi, E. Nakamura and I. Kuwajima, *Tetrahedron*, 1989, **45**, 349.
5 B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 1287.
6 (*a*) A. L. J. Beckwith, G. Phillipou and A. K. Serelis, *Tetrahedron Lett.*, 1981, **22**, 2811; (*b*) D. F. Taber, Y. Wang and S. J. Stachel, *Tetrahedron Lett.*, 1993, **34**, 6209.
7 (*a*) E. Schmitz, *Chem. Ber.*, 1958, **91**, 410; (*b*) A. J. Meskens, *Synthesis*, 1981, 501.
8 K. Sempuku, JP 92, 239/1981 (*Chem. Abstr.*, 1982, **96**, 6181p).
9 N. Iwasawa, M. Funahashi, S. Hayakawa and K. Narasaka, *Chem. Lett.*, 1993, 545.
10 (*a*) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1983, **105**, 651; (*b*) I. Ryu, S. Murai and N. Sonoda, *J. Org. Chem.*, 1986, **51**, 2389.
11 (*a*) A. L. J. Beckwith, D. M. O'Shea, S. Gerba and S. W. Westwood, *J. Chem. Soc., Chem. Commun.*, 1987, 666; (*b*) A. L. J. Beckwith, D. M. O'Shea and S. W. Westwood, *J. Am. Chem. Soc.*, 1988, **110**, 2565; (*c*) P. Dowd and S-C. Choi, *J. Am. Chem. Soc.*, 1987, **109**, 3493 and 6548.

Paper 5/02385H
Received 13*th April* 1995
Accepted 24*th May* 1995