Synthesis of 4,4-Disubstituted Cyclohexenones. Part 2.† Cycloaddition of 2-Chloroacrylonitrile to 5-Substituted 1,3-Dimethoxycyclohexa-1,4-dienes

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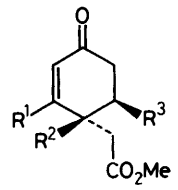
The cycloaddition of 2-chloroacrylonitrile to 1,3-dimethoxycyclohexadienes (**3**; R^1 = OMe, R^2 = H), derived by *in situ* conjugation of the Birch reduction products (**12**) produced from aromatic precursors (**11**) gave after acid work-up mainly bicyclo[2.2.2]octanone derivatives (**5**) and rearranged products (**13**). There is a strong preference for addition to the less hindered face of (**3**; R^1 = OMe, R^2 = H) [to give product (**5**) in which R^3 is *'syn'* to the carbonyl group], especially when the R^3 substituent is large, and there is also a preference for the CN group in (**5**) to be *'endo'*. This is illustrated most favourably in the formation of the cyclic acetals (**24**) produced by fluoride desilylation of the adducts (**5ix**) and (**5iy**) followed by acid cyclisation. Although the chloronitrile function in (**5**) could not be solvolysed (aqueous Na_2S) to the corresponding ketone, this conversion could be effected after the carbonyl group in (**5**) had been reduced to alcohol. Lithium t-butoxyaluminium hydride reduction of ketones (**5ax**) and (**5ay**) gave diols (**6ax**) and (**6ay**) respectively whereas borohydride reduction of ketone (**5bx**) gave the alcohols (**19a**) and (**19b**). Alcohols (**19a**), (**19b**), (**6ax**), and (**6ay**) were then converted respectively into ketones (**20a**) and (**20b**) [for (**19**)] and (**7a**) [for (**6**)]. Novel by-products in the sodium sulphide solvolysis of (**6ax**), (**6ay**) were the diols (**21aa**) and (**21ab**) which were shown to arise by reduction of (**7a**) in the presence of sodium sulphide. Jones oxidation of keto alcohol (**7a**) gave (**18a**) and oxidation of either keto alcohol (**20a**) or (**20b**) gave the same diketone (**18b**). Beckmann fragmentation of the corresponding oxime gave the cyclohexenone (**22**) thus establishing a formal route to cyclohexenones.

Cyclohexenones are useful intermediates in organic synthesis, as the recent work of Majetich [1] and Dauben [2] on the construction of fused, polycyclic systems demonstrates. Significant contributions in asymmetric synthesis have also been published by A. I. Meyers and co-workers.[3] Our own strategy for forming these compounds is outlined in Part 1, as are the results of Holmes and Madge on the synthesis of the compounds (**1**; R^1, R^2, and R^3 = H or Me).[4] Although this route provided an efficient method for the synthesis of these simple systems, the following limitations were observed; firstly the cycloaddition of the Birch reduction products (**2**) only proceeds well when R^2 = H or Me; secondly if R^1 and R^3 are not the same then conjugation of the diene (**2**) would necessarily lead to a mixture of isomers; lastly dienes such as (**3**; $R^1 = R^2$ = H, R^3 = alkyl) are not available by this route as the precursor (**2**; R^1 = alkyl, $R^2 = R^3$ = H) would isomerise to the more substituted isomer (**3**; R^1 = alkyl, $R^2 = R^3$ = H).



(**1**)

To circumvent this problem we planned to prepare dienes of the type (**2**; R^1 = OMe, R^2 = H, R^3 = alkyl). These should isomerise to the dienes (**3**; R^1 = OMe, R^2 = H, R^3 = alkyl). On reaction with 2-chloroacrylonitrile the latter were expected to give a mixture of *exo* and *endo* adducts (**4**; R^1 = alkyl, R^2 = H) in which the dienophile had approached the diene from the less hindered face. Hydrolysis of the enol ethers (**4**) would give the ketones (**5**). It was expected that reduction of the ketones (**5**) would occur from the less hindered face of the carbonyl to give the alcohols (**6**), which would give the ketone (**7**) on solvolysis. Baeyer–Villiger oxidation of the ketone (**7**) was expected to yield the keto ester (**8**) after methanolysis of the intermediate, as the tertiary, oxygen-bearing carbon should migrate preferentially (Scheme 1). To overcome the lack of reactivity of the dienes (**2**) and (**3**) when R^2 = H or Me, the diene (**10**) was to be prepared *via* the ketone (**9**). It was expected that by restraining the 4-substituent in a ring, its steric hindrance of attack of the dienophile on the diene would be considerably reduced. Subba Rao had previously demonstrated that this was the case with a carbocyclic ring fused on the diene,[5] and at the commencement of this work Masamune prepared the diene (**10**) and demonstrated that it reacted satisfactorily with methyl acrylate.[6]

3,5-Dimethoxytoluene (**11a**) was prepared in 97% yield by the reaction of 3-methyl resorcinol with dimethyl sulphate and potassium carbonate according to the method of Feutrill.[7] Reduction of the diether with lithium in an ethanol–liquid ammonia solvent gave the diene (**12a**) in 72% yield. When this diene was allowed to react with 2-chloroacrylonitrile in benzene under reflux a mixture of three of the stereoisomeric adducts (**5**; R^1, R^2 = Me, H; X, Y = CN, Cl) was obtained in 21% yield after hydrolysis of the enol ether intermediate. In addition two other compounds were obtained pure from the rather

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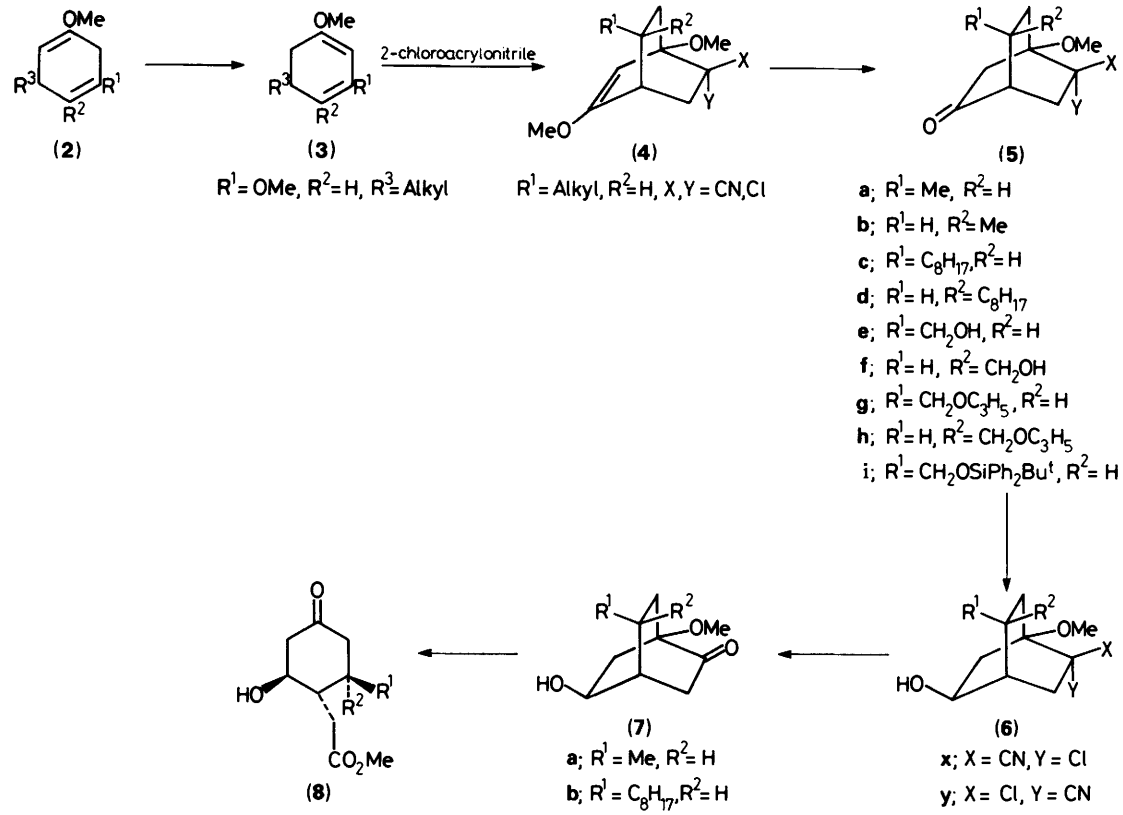
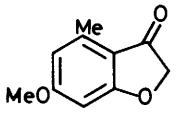


Scheme 1.



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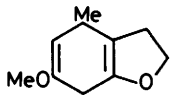
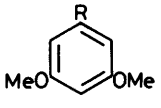


(10)

complex reaction mixture. The three adducts (**5ax**), (**5ay**), and (**5bx**) were shown to be present in a 3:1:1 ratio by ^{1}H NMR and GC analysis. Careful chromatography of the mixture achieved separation of one of the minor isomers, which was the polar component of the mixture, and also partially separated some of the major isomer from the mixture of the other two isomers.



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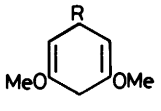
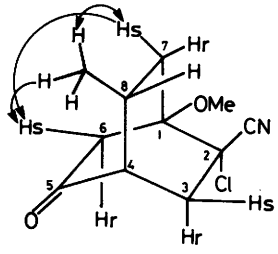


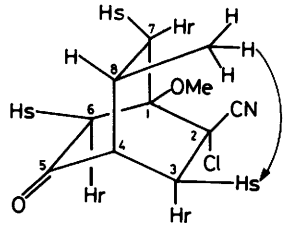
(12)

a; R = Me
b; R = C_8H_{17}
c; R = CH_2OH
d; R = $CH_2OSiMe_2Bu^t$
e; R = $CH_2OC_3H_5$
f; R = $CH_2OSiPh_2Bu^t$

The major isomer was deduced to be the *syn*, *exo* isomer (**5ax**), on the basis of NOE and decoupling experiments. Preliminary evidence for the *syn* stereochemistry of this adduct came from the fact that the proton H_{3r} showed no W-coupling to the proton H_8 in the ^{1}H NMR spectrum of the compound. Corroboration for this came from the irradiation of the signal due to the methyl group. This led to an enhancement of the signals due to H_{7s} and H_{6s}, but not to those of H_{7r} and H_{3s}. Similarly irradiation of the signals due to H_{7s} led to an enhancement of the signals due to H_{6s} and the methyl group. As H_{7r} could be easily distinguished from H_{7s}, and H_{6s} from H_{6r}, because of the W-coupling between H_{6r} and H_{7r}, these results confirm that the methyl group is *syn* to the ketone. The stereochemistry at C-2 is discussed below.



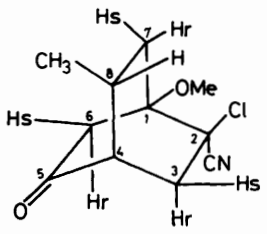
(5ax)



(5bx)

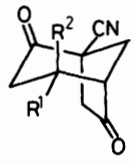
The minor isomer that could be obtained pure was assigned the *anti* structure (**5bx**) as irradiation of the signal due to the methyl group in the ^{1}H NMR spectrum gave a large enhancement of the signals due to H_{3s} and H_{7r}, and none of the signals due to H_{7s} and H_{6s}. Although the other minor isomer could not be obtained free of the ketone (**5ax**) it was tentatively assigned the structure (**5ay**) on the basis of the chemical shifts of the protons on C-8. In both the ketones (**5ax**) and (**5bx**) the proton on C-7 on the same side of the bridge as the methyl group is shielded relative to all the other protons of the bicyclic system. In the spectrum of the ketone (**5ay**) the shielded proton is a double doublet, suggesting that it is H_{7s} and not H_{7r} as H_{7r} should have an additional, W-coupling. Therefore the compound is the *syn*, *endo* isomer as drawn.

The two other compounds isolated were the diketones (**13a**) and (**13b**). Raphael *et al.*[8a] had observed a similar



(5ay)

rearrangement of the compound (**14**) to the ketone (**15**), although in this case much higher temperatures were required to effect the conversion. It is believed that the *endo* intermediates (**4**) can rearrange, assisted by the enol ether oxygen lone pair (Scheme 2). The tricyclic intermediate (**16**) can collapse to the [3.2.1] system (**17**) which on hydrolysis gives the observed diketones.[9] If this mechanism is correct only the *endo* isomers should rearrange. [In a related system it has indeed been found that only one isomer rearranges and an analogue of the tricyclic



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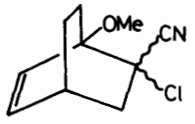
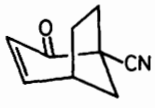


(14)

a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Me
c; $R^1 = C_8H_{17}$, R^2 = H
d; R^1, R^2 = H, CH_2OH
e; $R^1 = CH_2OC_3H_5$, R^2 = H
f; R^1 = H, $R^2 = CH_2OC_3H_5$

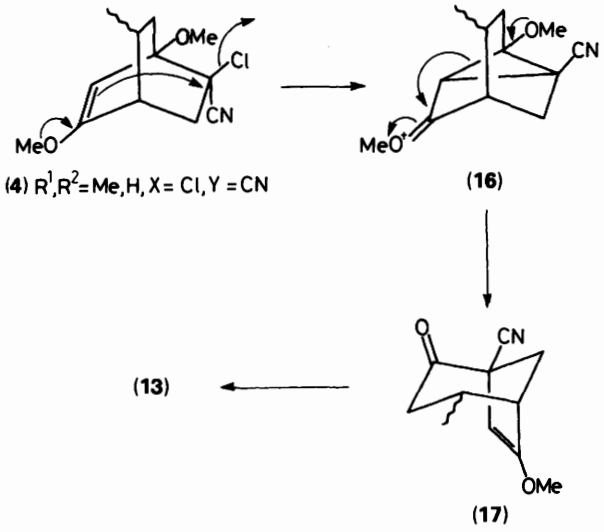


(15)

intermediate (**16**) has been isolated (see following paper).] For this reason it is believed that the major Diels–Alder adducts isolated, which are not susceptible to this rearrangement, are the *exo* nitriles. A possible reason that the *anti*, *endo* isomer (**4by**) completely rearranges, while the *syn*, *endo* isomer (**4ay**) is consumed much more slowly, is that in the former the rearrangement relieves the steric interaction between the methyl group and H_{3s}, while in the latter there is no such interaction as the methyl group lies over the sp^2 carbons of the enol ether.

As the rearrangement is unimolecular, while the Diels–Alder reaction is bimolecular it seemed it might be possible to suppress the former by speeding up the latter. However use of Lewis Acids,[10] partially isomerised diene,[11] aqueous solvent[12] or ultrasound did not lead to any improvement in the reaction, and sometimes caused it to take a different path. It was possible to raise the yield of the adducts (**5ax**) to 60% by running the reaction in neat 2-chloroacrylonitrile at 65 °C. Under these conditions the ratio (**5ax**):(**5ay**):(**5bx**) was 3:1:1 (isolated in 49% yield after separation) and the rearranged products (**13**) were obtained in 12% yield (1:1 ratio).

To confirm the stereochemical assignments the diketones (**18a**) and (**18b**) were prepared. None of the adducts (**5ab**) gave



(4) R^1,R^2 = Me,H, X = Cl, Y = CN

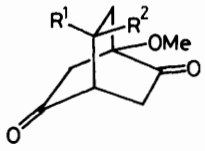
(16)

(13)

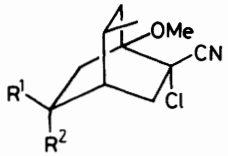
(17)

Scheme 2.

any detectable amount of either diketone when treated with either sodium sulphide (1 mol equiv. $Na_2S{\cdot}9H_2O$, 2 mol equiv. KOH in 95% EtOH–H_2O)[13] or potassium hydroxide in DMSO.[14] Reduction of the ketone (**5bx**) with $NaBH_4$ at 0 °C

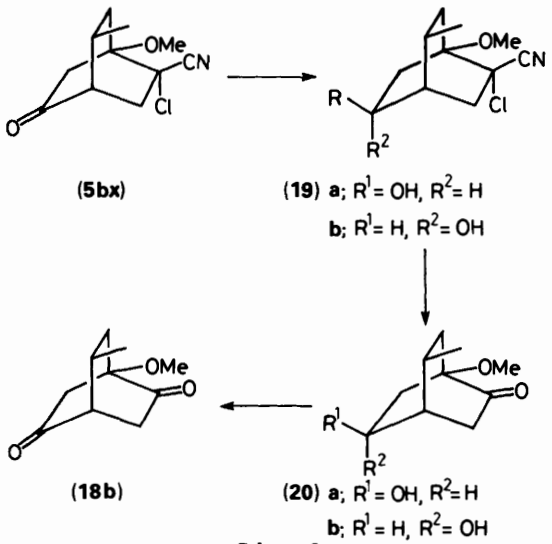


(18) **a**; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Me



(19) **a**; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH

gave the alcohols (**19a**) and (**19b**) in 93% yield. Solvolysis (1 mol equiv. $Na_2S{\cdot}9H_2O$, 2 mol equiv. KOH in 95% EtOH–H_2O) of (**19a**) gave (**20a**) in 38% yield, and of (**19b**) gave (**20b**) in 40% yield. Oxidation of either alcohol with Jones' reagent gave the diketone (**18b**) in 60% yield (Scheme 3).



(5bx)

(19) **a**; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH

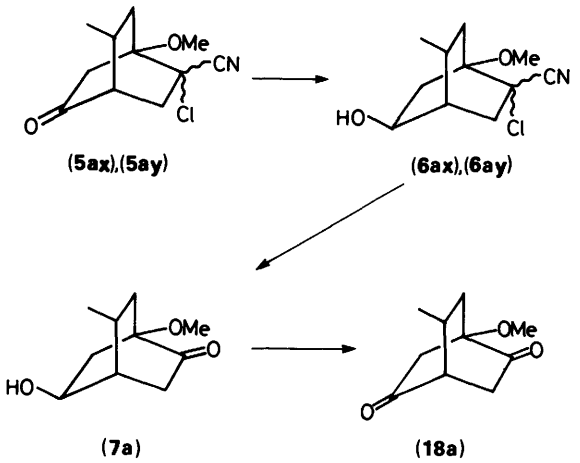
(18b)

(20) **a**; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH

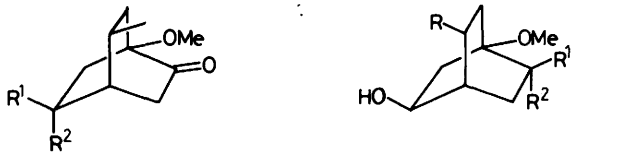
Scheme 3.

The mixture of ketones (**5ax**) and (**5ay**) was reduced to a single pair of diols (**6ax**) and (**6ay**) with lithium tri-t-butoxyaluminium hydride. Solvolysis of this mixture under the

usual conditions gave a single keto alcohol (**7a**; R^1 = Me, R^2 = H) in 40–50% yield, confirming that the stereochemistry of C-8 is the same in (**5ax**) and (**5ay**). Oxidation of (**7a**) with Jones' reagent gave the diketone (**18a**) in 60% yield (Scheme 4). A series of NOE experiments confirmed the stereochemistry assigned to this compound.



Scheme 4.



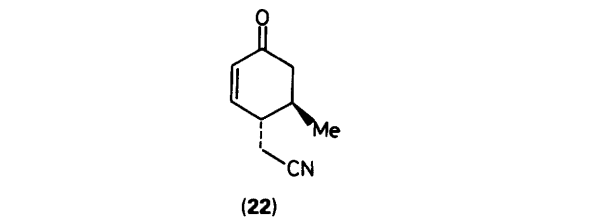
(**20**) **a**; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH

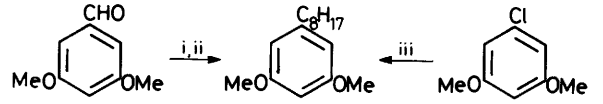
(**21**) **aa**; R^1 = OH, R^2 = H, R = Me
ab; R^1 = H, R^2 = OH, R = Me
ba; R^1 = OH, R^2 = H, R = C_8H_{17}
bb; R^1 = H, R^2 = OH, R = C_8H_{17}

In the solvolysis reaction of the chloronitriles (**6ax**) and (**6ay**) an additional pair of products was observed. These were assigned the structures (**21aa**) and (**21ab**). To confirm this assignment the keto alcohol (**7a**) was treated with sodium borohydride. This also gave (**21aa**) and (**21ab**), but in a slightly different ratio. Resubjection of the keto alcohol (**7**) to the solvolysis conditions caused a slow reduction to the diols, with a very similar product distribution after a given reaction time to that observed in the original solvolysis. This suggests that the keto alcohol is an intermediate in the formation of the diols (**21**) from the chloronitriles (**6a**). Such a reduction of ketones with sodium sulphide has not been observed before, although recently this reagent has been reported to reduce aromatic aldehydes.[15] Some further observations on this reaction are discussed below.

The strategy for production of hydroxylated cyclohexanone derivatives calls for Baeyer–Villiger oxidation of bicyclo-[2.2.2]octanones of type (**7**). When the keto alcohol (**7a**) was treated with a variety of peracids, and the reaction worked up with methanol and acid, or with dimethyl sulphate, the required hydroxycyclohexanone ester (**8a**; R^1 = Me, R^2 = H) was isolated in very low yield. As an alternative to the Baeyer–Villiger fragmentation reaction, the Beckmann rearrangement route developed by Raphael[8a] and others[8b] was examined. This proved more satisfactory, and after treatment of the ketone (**7a**) with NH_2OH·HCl in EtOH–H_2O, then treatment of the resulting oxime with NaH (2 mol equiv.) then toluene-*p*-sulphonyl chloride, the enone (**22**) was isolated in 58% yield.

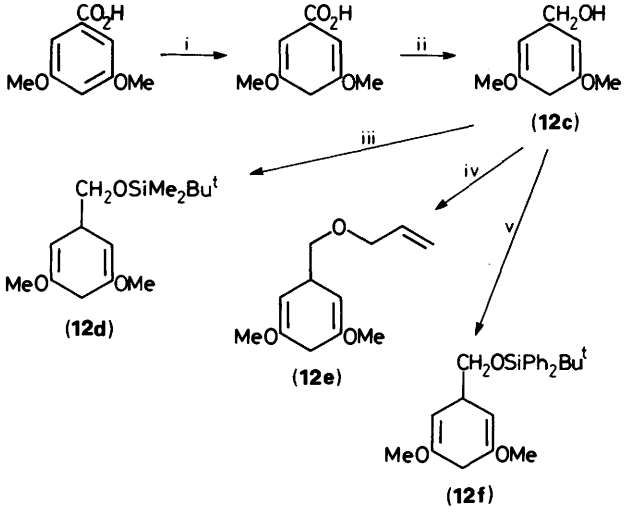
The rearrangement of the initially formed *endo* bicyclo[2.2.2] adduct to the bicyclo[3.2.1] compound has been a problem in all of the cases that we have examined except for one. The octyl substituted diene (**12b**), was prepared from the aromatic precursor whose synthesis is shown in Scheme 5. Cycloaddition





Scheme 5. *Reagents:* i, $Ph_3P{=}CHC_6H_{13}$ (87%); ii, H_2/Pt (83%); iii, $C_8H_{17}MgBr$–Li_2CuCl_4[16] (61%).

of 2-chloroacrylonitrile to (**12b**) gave a 50% yield of (**5cx**), (**5cy**), and (**5dx**) in a 15:5:1 ratio, along with 9% of a single rearrangement product (**13c**). Large alkyl substituents on the ethano-bridge of the diene evidently increase the face selectivity of the cycloaddition as expected. The hydroxymethyl protected dienes (**12d**) and (**12e**) were prepared as shown in Scheme 6. The



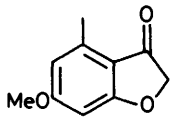
Scheme 6. *Reagents:* i, Li, NH_3[17] (99%); ii, $LiAlH_4$[18] (79%); iii, Bu^tMe_2SiCl, imidazole (100%); iv, Allyl bromide, NaH (92%); v, Bu^tPh_2SiCl, imidazole (96%).

silyl-protected (**12d**) gave 24% of (**5ex**) and a 7% combined yield of (**13d**) as a mixture of epimers along with 3% of the ether (**23**). The allyl-protected (**12e**) gave the ethers (**5gx**), (**5gy**), and (**5hx**)

Table. Cycloaddition of 2-chloroacrylonitrile to dienes (**12**).

Diene (**12**)	Yield (%) of [2.2.2]adduct (**5**)	Ratio of isomers (**5**)	Yield (%) of [3.2.1]adduct (**13**)
a; R = Me	60	(**5ax**):(**5ay**):(**5bx**) = 3:1:1	12 (**13a, b**)
b; R = C_8H_{17}	50	(**5cx**):(**5cy**):(**5dx**) = 15:5:1	9 (**13c**)
c; R = CH_2OH	complex mixture	—	—
d; R = $CH_2OSiMe_2Bu^t$	24	(**5ex**):(**5ey**) = 8:1	8 (**13d**)[a]
e; R = $CH_2OC_3H_5$	27	(**5gx**):(**5gy**):(**5hx**) = 9:1:2	28 (**13e**):(**13f**) = 3:1
f; R = $CH_2OSiPh_2Bu^t$	48[b]	(**24x**):(**24y**) = 3:1	—

[a] The acetal (**23**) was also isolated (4%). [b] Isolated as acetals (**24**).



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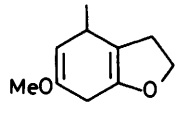

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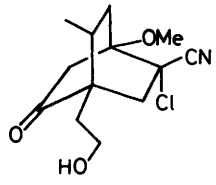
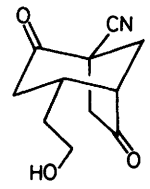
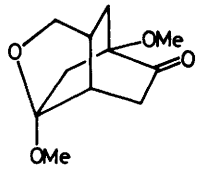


(**25**)

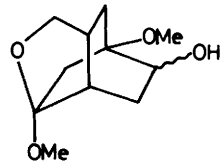


(**26**)



(**27**)

Elaboration of the adducts (**24**) and (**5cx**) was examined. Reduction of (**5cx**) with sodium borohydride or lithium tri-t-butoxyaluminium hydride gave the single alcohol (**6cx**) in 97% yield. Solvolysis of this under the usual conditions gave the ketoalcohol (**7b**) in 21% yield, plus a 15% yield of the diols (**21ba**) and (**21bb**). Once again reduction of the ketone (**7b**) with sodium borohydride gave the same diols as were obtained from the solvolysis. It was suggested that hydride-transfer from the solvent was responsible for the reduction in a process akin to the Meerwein–Ponndorf reaction. Unfortunately this proved not to be the case as using Bu^tOH as the reaction solvent gave a similar product distribution, although in much lower yield, and in a slower reaction. (The Bu^tOH would have been incapable of providing a source of hydride ions.) Similarly, reaction of the ketals (**24**) under the sodium sulphide hydrolysis conditions gave the ketone (**27**) in 25% yield and the alcohols (**28**) in 23% yield.



(**28**)

in 27% yield in a 9:1:2 ratio and the rearranged products (**13e**) and (**13f**) in a 28% yield and a 3:1 ratio (Table). Originally it appeared that (**5ex**) was a mixture of compounds. However reduction with $NaBH_4$ gave a single alcohol (**6ex**) in 82% yield. It therefore appears that (**5ex**) exists in equilibrium with its hemiacetal. Use of the t-butyldiphenylsilyl protecting group[19] as in the diene (**12f**) proved the most efficacious. Thus the diene (**12f**) gave a respectable yield of adducts with total *syn*-selectivity and strong *endo*-selectivity. In this case it was possible to deprotect the silyl group of (**5ix**) and (**5iy**) (1.1 equiv. TBAF, THF, 0 °C)[20] and cyclise the resultant alcohol on to the enol ether of the adducts (*p*-TsOH). In this way the acetals (**24**) were obtained in 48% combined yield from the diene (**12f**) in a 3:1 ratio.

The bicyclic diene (**10**) was prepared by lithium/ammonia reduction of 6-methoxy-4-methyl-2,3,4,7-tetrahydrobenzofuran which was obtained by reduction of the ketone (**9**).[6] After cycloaddition with 2-chloroacrylonitrile the resulting enol ether adduct was hydrolysed with dilute acid. A modest 11% yield of the adduct (**25**) and 8% of the rearranged product (**26**) could be obtained. The former appeared to be essentially one isomer, presumably that shown, although it was contaminated with some of the rearrangement product (**26**) with which it co-eluted. The product (**26**) was obtained pure, as a single isomer, by fractional crystallisation of the mixture of (**25**) and (**26**). It appears that, in agreement with the results of Masamune,[6] the stereoselectivity of the cycloaddition improves when the second ring is fused onto the diene.

In summary the preparation of bicyclo[2.2.2]octanones by cycloaddition reaction of 1,3-dimethoxycyclohexa-1,4-dienes with 2-chloroacrylonitrile is complicated by the rearrangement of the initially formed *endo* adducts to the bicyclo[3.2.1]-octanone system. When the original diene has a large 5-substituent there is a strong preference for formation of the *syn* product, in which the dienophile has reacted with the less hindered face of the diene. Elaboration of the adduct is complicated by the unexpected conversion of the chloronitrile intermediates into alcohols under the usual solvolysis reaction conditions, a reaction in which the expected ketone is likely to be an intermediate. Although it is possible to prepare the required substituted cyclohexenones by this route, the efficacy is frustrated by the modest yields. Therefore the alternative methods described in the following paper have been examined.

Experimental

IR spectra were recorded on a Perkin-Elmer 297 or 983 grating spectrophotometer using either a 2.5% w/v solution in 0.1 mm solution cells or liquid film. ^1H NMR spectra were recorded on a Varian EM 360A (60 MHz) or EM 390 (90 MHz) or Bruker WP 80 (80 MHz) or WM 250 (250 MHz) instrument using either $SiMe_4$ or $CHCl_3$ as internal standard. ^{13}C NMR spectra were recorded on a Bruker WM 250 (63 MHz) instrument using the solvent as internal reference. Mass spectra were determined using MS 902 or MS 30 instruments. CI mass spectra were recorded at ICI Pharmaceuticals Division. Analytical TLC was

carried out on Merck pre-coated glass plates containing a 0.25 mm thick layer of silica gel 60 GF_{254} or aluminium oxide 150 F_{254} (type T). Gravity and flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). Melting points were recorded on a Kofler hot-stage apparatus. Microanalyses were carried out by Mr. D. Flory and staff at the University Chemical Laboratory.

1,3-*Dimethoxy*-5-*methylcyclohexa*-1,4-*diene* (**12a**).—3,5-Dimethoxytoluene (**11a**)[7] (20 g, 132 mmol) was dissolved in ethanol (120 ml) and liquid ammonia (500 ml). Lithium wire (8.1 g, 1.16 mmol) was added in lengths of approximately 0.5 g in weight so as to maintain the blue colour of the solution. After completion of this process the liquid ammonia was evaporated under a stream of nitrogen. Saturated ammonium chloride solution was added to neutralise the residues, and the resulting solution was extracted with dichloromethane (3 × 200 ml). The organic extracts were combined and dried (Na_2SO_4) and after filtration and evaporation the *product* (**12**) was obtained as an oil (14.5 g, 72%), b.p. 38–40 °C/0.5 mmHg; $\nu_{max}(CHCl_3)$ 3 040w, 2 980w, 2 940s, 2 820m, 1 680s, 1 650m, 1 395s, 1 230s, 1 200s, 1 150s, 1 030m, and 820m cm^{-1}; $\delta_H(CDCl_3, 90\ MHz)$ 4.6 (2 H, d, *J* 4 Hz, C*H*=COMe), 3.6 (6 H, s, OCH_3), 3.1 (1 H, tq, *J* 4, 7 Hz, C*H*CH_3), 2.9–2.8 (2 × d, *J* 8 Hz, CH_2), and 1.1 (3 H, d, *J* 7 Hz, CHCH_3); *m/z* 154 (M^+, 22%), 152 (100), 139 (38), 123 (72), 109 (21), 91 (21), and 77 (21); (Found: C, 69.8; H, 9.1%; M^+, 154.1006. $C_9H_{14}O_2$ requires C, 70.1; H, 9.2%; *M*, 154.0994).

(1R*,2R*,8S*)-, (1R*,2S*,8S*)-, *and* (1R*,2R*,8R*)-2-*Chloro*-1-*methoxy*-8-*methyl*-5-*oxobicyclo*[2.2.2]*octane*-2-*carbonitrile* (**5ax**), (**5ay**), *and* (**5bx**), *and* (1R*,4R*) *and* (1R*,4S*)-4-*Methyl*-2,6-*dioxobicyclo*[3.2.1]*octane*-1-*carbonitrile*, (**13b**) *and* (**13a**).—The diene (**12a**) (7.0 g, 45.5 mmol) was heated with 2-chloroacrylonitrile (25 ml) under an argon atmosphere at 65 °C for 90 min. After this period the solution was poured onto a mixture of tetrahydrofuran (THF) and 3M hydrochloric acid (150 ml, 1:1 mixture) which was stirred at r.t for 2 d. This mixture was then neutralised by addition of solid sodium carbonate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 100 ml) and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (500 g) with 20% ethyl acetate–hexane (500 ml), then 30% ethyl acetate–hexane (7.5 l), and then 75% ethyl acetate–hexane (2.5 l) as eluant, taking 50 ml fractions. Spectral analysis of the compounds obtained from fractions 1–65 showed that these were not the desired ketones. Fractions 66–85 contained the two *syn*-isomers (**5ax**) and (**5ay**) plus a trace of impurity. These fractions were combined and repurified by chromatography on silica (250 g) with 30% ethyl acetate–hexane as eluant to give the two *syn* isomers (**5ax**) and (**5ay**) (3.0 g, 29%) as prisms, m.p. 55.5–56.5 °C. The major isomer (**5ax**) (0.1 g) could be obtained pure by combining the first and last fractions of the recolumned material.

Fractions 102–131 contained the *anti* isomer (**5bx**) which was obtained as prisms, m.p. 73.5–75.0 °C, (1.25 g, 12%). The diketone (**13b**) (0.49 g, 6%) was obtained from fractions 164–180 as prisms, m.p. 143.5–145 °C and the diketone (**13a**) (0.47 g, 6%) was obtained as prisms, m.p. 116–118 °C from the fractions 192–201.

syn,exo-*Isomer* (**5ax**); $\nu_{max}(CHCl_3)$ 2 950s, 2 250w, 1 730s, and 1 600m cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 3.41 (3 H, s, OCH_3), 2.90–2.97 (1 H, dd, *J* 15.6, 3.0 Hz, H_{3s}), 2.77–2.86 (1 H, dd, *J* 18.7, 3.6 Hz, H_{6r}), 2.48–2.54 (1 H, dd, *J* 15.6, 2.5 Hz, H_{3r}), 2.46–2.51 (1 H, d, *J* 18.7 Hz, H_{6s}), 2.20–2.30 (3 H, m, H_4, H_{7r}, H_8), 1.58–1.66 (1 H, dd, *J* 13.6, 5.4 Hz, H_{7s}), and 1.01–1.03 (3 H, d, *J* 6.8 Hz, CH_3); *m/z* 227 (M^+, 10%), 212 (8), 192 (4), and 112 (100); (Found: M^+, 227.0721. $C_{11}H_{14}ClNO_2$ requires *M*, 227.0714).

syn,endo-*Isomer* (**5ay**); $\delta_H(CDCl_3, 250\ MHz)$ 3.40 (3 H, s, OCH_3), 1.32–1.40 (1 H, dd, *J* 12.9, 6.2 Hz), and 0.98–1.00 (3 H, d, *J* 6.5 Hz, CH_3). Other signals obscured by those of isomer (**5ax**).

anti-exo-*Isomer* (**5bx**); $\nu_{max}(CHCl_3)$ 2 940m, 2 250w, 1 730s, 1 600m, and 1 120s cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 3.38 (3 H, s, OCH_3), 3.01–3.09 (1 H, dd, *J* 16.0, 2.2 Hz, H_{3s}), 2.77–2.86 (1 H, dd, *J* 18.5, 3.3 Hz, H_{6r}), 2.57–2.64 (1 H, d, *J* 18.5 Hz, H_{6s}), 2.41–2.49 (1 H, dt, *J* 16.0 Hz, 1.1 Hz, H_{6r}), 2.1–2.4 (3 H, m, H_4, H_{7s}, and H_8), 1.56–1.67 (1 H, ddd, *J* 14.1, 6.6, 3.3 Hz, H_{7r}), and 1.16–1.18 (1 H, d, *J* 6.8 Hz); $\delta_C(CDCl_3, 62.9\ MHz)$ 206.8 (C-5), 118.6 (CN), 78.7 (C–O), 61.2 (C-1), 51.3, 47.8, 40.8, 37.7, 33.7, 26.5, and 18.7; *m/z* 227 (M^+, 12%), 212 (7), 192 (3), and 112 (100); (Found: C, 57.8; H, 5.9; N, 6.1. $C_{11}H_{14}ClNO_2$ requires C, 58.0; H, 6.2; N, 6.2%).

Diketone (**13b**); $\nu_{max}(CHCl_3)$ 2 250w, 1 760s, 1 730s, and 1 600m cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 2.85–2.92 (1 H, d, *J* 18.6 Hz, H_7), 2.71–2.79 (1 H, dd, *J* 18.6, 2.5 Hz, H_7), 2.53–2.68 (4 H, m, H_{3r}, H_{3s}, H_5, and H_8), 2.43–2.52 (1 H, m, H_4), 2.29–2.36 (1 H, d, *J* 16.4 Hz, H_8), and 1.11–1.14 (3 H, d, *J* 7.0 Hz, CH_3); $\delta_C(CDCl_3, 62.9\ MHz)$ 210.7, 199.2, 116.9, 50.4, 50.3, 45.4, 41.2, 34.5, 31.1, and 19.2; *m/z* 177 (M^+, 11%), 152 (9), 122 (18), 98 (81), and 81 (100); (Found: C, 67.5; H, 6.3; N, 7.7. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%).

Diketone (**13a**); $\nu_{max}(CHCl_3)$ 2 250w, 1 755s, 1 735s, and 1 600w cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 2.81–2.88 (1 H, d, *J* 18.8 Hz, H_7), 2.54–2.78 (4 H, m), 2.37–2.43 (1 H, dd, *J* 12.7, 2.9 Hz), 2.03–2.24 (2 H, m), and 1.08–1.11 (3 H, d, *J* 6.4 Hz, CH_3); $\delta_C(CDCl_3, 62.9\ MH_3)$ 209.0, 198.7, 117.0, 50.1, 49.5, 45.9, 42.5, 39.7, 34.9, and 18.5; (Found: C, 67.8; H, 6.3; N, 7.7. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%).

(1R*,2R*,5R*,8R*)-2-*Chloro*-5-*hydroxy*-1-*methoxy*-8-*methylbicyclo*[2.2.2]*octane*-2-*carbonitrile* (**19a**) *and* (1R*,2R*,5S*,-8R*)-2-*Chloro*-5-*hydroxy*-1-*methoxy*-8-*methylbicyclo*[2.2.2]-*octane*-2-*carbonitrile* (**19b**).—The ketone (**5bx**) (0.184 g, 0.81 mmol) was dissolved in methanol (1 ml) and the solution was cooled to 0 °C. Sodium borohydride (33 mg) in methanol (1 ml) was added dropwise to the solution, which was stirred at room temperature for 1 h after addition was completed before a further portion of sodium borohydride (16 mg) was added. The solution was stirred at room temperature for a further hour and then 3M hydrochloric acid was added until the pH of the mixture reached 2–3. The solvent was then evaporated under reduced pressure and the solid residue was partitioned between water (10 ml) and ethyl acetate (20 ml). The aqueous phase was extracted with ethyl acetate (3 × 20 ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a solid residue. This was purified by flash column chromatography on silica (20 g) with 50% ethyl acetate–hexane as eluant. This gave the alcohol (**19a**) (70 mg, 38%) as an oil, and the alcohol (**19b**) (102 mg 55%) also as an oil.

Alcohol (**19a**); $\nu_{max}(CHCl_3)$ 3 200–3 600s, 2 250w, and 1 120s cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$, 4.24–4.31 (1 H, ddd, *J* 9.3, 5.3, 2.4 Hz, H_5), 3.32 (3 H, s, OCH_3), 2.81–2.88 (1 H, dd, *J* 15.9, 3.6, 2.4 Hz, H_{3s}), 2.38–2.47 (1 H, dd, *J* 13.5, 9.5 Hz, H_{7s}), 2.40–2.50 (1 H, m, H_8), 2.32–2.40 (1 H, ddd, *J* 15.3, 5.3, 3.4 Hz, H_{6r}), 2.23–2.32 (1 H, ddd, *J* 15.9, 1.6 Hz, H_{3r}), 1.61–1.68 (1 H, dd, *J* 13.3, 5.3 Hz, H_{6s}), 1.60–1.70 (1 H, br s, OH), 1.50–1.56 (1 H, m, H_4), 1.22–1.31 (1 H, ddd, *J* 13.5, 7.3, 3.4 Hz, H_{7r}), and 1.03–1.06 (3 H, d, *J* 6.8 Hz, CH_3); *m/z* 229 (M^+, 0.8%), 214 (8), 149 (13), 137 (15), and 100 (100); (Found: M^+, 229.0865. $C_{11}H_{16}ClNO_2$ requires *M*, 229.0869).

Alcohol (**19b**); $\nu_{max}(CHCl_3)$ 3 200–3 600s cm^{-1}; $\delta_H(CDCl_3,$

250 MHz) 4.04–4.11 (1 H, dt, *J* 9.7, 2.7 Hz, H_5), 3.33 (3 H, s, OCH_3), 2.76–2.77 (2 H, d, *J* 2.5 Hz, H_{3r} and H_{3s}), 2.27–2.21 (1 H, dd, *J* 13.9, 10.0, H_{7s}), 2.12–2.21 (1 H, dd, *J* 14.6, 9.7 Hz, H_{6s}), 1.81–1.94 (1 H, ddd, *J* 14.6, 3.4, 2.7 Hz, H_{6r}), 1.5–1.8 (2 H, m, OH and H_8), 1.37–1.46 (1 H, ddd, *J* 13.9, 5.3, 3.4 Hz, H_{7r}), and 1.12–1.14 (3 H, d, *J* 7.0 Hz, CH_3); *m/z* 229 (M^+, 0.9%), 214 (6), 149 (44), 100 (74), and 72 (100); (Found: C, 57.2; H, 6.9; N, 5.9. $C_{11}H_{16}ClNO_2$ requires C, 57.5; H, 7.0; N, 6.1%).

(1R*,5R*,8R*)-5-*Hydroxy*-1-*methoxy*-8-*methylbicyclo*-[2.2.2]*octan*-2-*one* (**20a**).—The alcohol (**19a**) (70 mg, 0.31 mmol), sodium sulphide (100 mg) and potassium hydroxide (25 mg) were dissolved in 95% ethanol (2 ml) and the solution was heated under reflux for 48 h. The solvent was then evaporated under reduced pressure and the solid residue was divided between water (5 ml) and ethyl acetate (5 ml). The aqueous phase was extracted with ethyl acetate (2 × 5 ml) and was then acidified with 2M hydrochloric acid and extracted with ethyl acetate (2 × 5 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (5 ml) and brine (5 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield an oil. This was purified by flash column chromatography on silica (10 g) with 50% ethyl acetate–hexane as eluant to give the *ketone* (**20a**) (21 mg, 38%) as an oil; ν_{max}($CHCl_3$) 3 650w, 3 200–3 500br, 2 950s, 1 730s, and 1 600m cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.32–4.41 (1 H, ddd, *J* 9.5, 4.5, 2.1 Hz, H_5), 3.26 (3 H, s, OCH_3), 2.26–2.42 (2 H, m, H_3), 1.74–2.03 (4 H, m, H_{6r}, H_{6s}, H_{7s}, and H_8), 1.7 (br, OH), 1.50–1.61 (1 H, ddd, *J* 13, 6, 2 Hz, H_{7r}), 1.42–1.44 (1 H, m, H_4), and 0.98–1.01 (3 H, d, *J* 7.0 Hz, CH_3); *m/z* 184 (M^+, 1.6%), 166 (1), 140 (81), 123 (64), 113 (73), and 55 (100); (Found: M^+, 184.1102. $C_{10}H_{16}O_3$ requires *M*, 184.1099).

(1R*,5S*,8R*)-5-*Hydroxy*-1-*methoxy*-8-*methylbicyclo*-[2.2.2]*octan*-2-*one* (**20b**).—The alcohol (**19b**) (85 mg, 0.37 mmol), sodium sulphide nonahydrate (170 mg), and potassium hydroxide (28 mg) were dissolved in 95% ethanol (2 ml) and the solution was heated under reflux for 48 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (5 ml) and ethyl acetate (5 ml). The aqueous phase was extracted with ethyl acetate (2 × 5 ml) and was then acidified with 2M hydrochloric acid and extracted with ethyl acetate (2 × 5 ml) again. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (5 ml), and brine (5 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give an oil. This was purified by chromatography on silica gel (10 g) with 50% ethyl acetate–hexane as eluant to give the *ketone* (**20b**) (28 mg, 40%) as an oil; ν_{max}($CHCl_3$) 3 100–3 600br, 2 900s, 1 725s, and 1 600m cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.06–4.12 (1 H, m, H_5), 3.21 (3 H, s, OCH_3), 2.77–2.85 (1 H, ddd, *J* 11.6, 4.5, 2.6 Hz, H_{3r}), 2.25–2.33 (1 H, ddt, *J* 11.8, 1.0, 3.4 Hz, H_{3s}), 1.8–2.2 (5 H, m, OH, $H_{6r,s}$, H_{7s}, and H_8), 1.69–1.79 (1 H, dt, *J* 11.8, 2.9 Hz, H_{7r}), 1.49–1.51 (1 H, m, H_4), and 1.01–1.04 (3 H, d, *J* 6.5 Hz, CH_3); *m/z* 184 (M^+, 1%), 156 (14), 140 (56), and 100 (100); (Found: M^+, 184.1110. $C_{10}H_{16}O_3$ requires *M*, 184.1099).

(1R*,8R*)-1-*Methoxy*-8-*methylbicyclo*[2.2.2]*octane*-2,5-*dione* (**18b**).—The alcohol (**20b**) (11.1 mg, 0.06 mmol) was dissolved in acetone (1 ml) and the solution was cooled to 0 °C. Jones' reagent was added to the solution dropwise by pipette until the solution became orange. Isopropyl alcohol was added to the suspension until the solution became green, when acetone (5 ml) was added. The solution was then filtered through a pad of Celite and the pad was washed twice with acetone. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica (1 g) with 50% ethyl acetate–hexane as eluant to give the *ketone* (**18b**) (6.6 mg, 60%) as an oil; ν_{max} 1 725s and 1 100s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 3.29 (s, OCH_3), 2.97–3.05 (1 H, ddd, *J* 11.6, 4.9, 2.3 Hz, H_4), 2.64–2.73 (1 H, dd, *J* 18.7, 3.0 Hz, H_{6r}), 2.52–2.60 (1 H, dd, *J* 18.7, 2.3 Hz, H_{6s}), 2.42–2.52 (1 H, ddd, *J* 11.6, 3.0, 2.5 Hz, H_{3s}), 2.08–2.22 (2 H, m, H_{7r} and H_8), 1.90–2.00 (1 H, m, H_{3r}), 1.18–1.22 (1 H, dd, *J* 12.0, 2.9 Hz, H_{7s}), and 1.08–1.11 (1 H, d, *J* 6.4 Hz, CH_3); *m/z* 182 (2), 154 (8), 139 (54), 97 (50), and 55 (100); (Found: M^+, 182.0955. $C_{10}H_{14}O_3$ requires *M*, 182.0943).

(1R*,2R*,5R*,8S*)- *and* (1R*,2S*,5R*,8S*)-2-*Chloro*-5-*hydroxy*-1-*methoxy*-8-*methylbicyclo*[2.2.2]*octane*-2-*carbonitrile* (**6ax**) *and* (**6ay**).—The ketones (**5ax**) and (**5ay**) (100 mg, 0.44 mmol) were dissolved in THF (5 ml) and the solution was added to a slurry of lithium (tri-t-butoxy)aluminium hydride (450 mg) in dry THF (10 ml) at −78 °C over 15 min. The mixture was allowed to warm to room temperature overnight before the reducing agent was quenched by addition of water (1 ml). The solvent was evaporated under reduced pressure and the solid residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The aqueous layer was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a solid residue. This was purified by flash column chromatography on silica (10 g) with 50% ethyl acetate–hexane as eluant to give the mixture of *alcohols* (**6ax**) and (**6ay**) (95 mg, 95%) as needles, m.p. 63–65 °C; ν_{max}($CHCl_3$) 3 650s, 3 350br, 2 920s, 2 820m, 2 240w, 1 600w, 1 320s, and 1 125s, cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.26–4.29 (1 H, m, H_5), 3.37 (3 H, s, OCH_3), 2.65–2.73 (1 H, dd, *J* 15.1, 3.8 Hz, H_3), 2.33–2.45 (2 H, m, H_3 and H_6), 2.16–2.27 (3 H, m, H_4, H_6, and H_8), 1.72–1.85 (2 H, m, H_{8r} and H_{8s}), 1.6 (1 H, s, OH), and 1.29–1.32 (3 H, d, *J* 6.8 Hz, CCH_3); *m/z* 214 ($M^+ - CH_3$, 2%), 210 (1), 198(1), 181 (2), 176 (1), 149 (2), 100 (78), and 72 (100); (Found: C, 57.6; H, 7.2; N, 6.2. $C_{11}H_{16}ClNO_2$ requires C, 57.5; H, 7.0; N, 6.1%).

(1R*,5R*,8S*)-5-*Hydroxy*-1-*methoxy*-8-*methylbicyclo*-[2.2.2]*octan*-2-*one* (**7a**).—The chloronitriles (**6ax**) and (**6ay**) (92 mg, 0.40 mmol), sodium sulphate nonahydrate (190 mg) and potassium hydroxide (35 mg) were heated under reflux in 95% ethanol (2 ml) for 22 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (10 ml) and ethyl acetate (10 ml). The aqueous layer was extracted with ethyl acetate (2 × 10 ml) and was then acidified with 2M hydrochloric acid and extracted with ethyl acetate (2 × 10 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oil. This was purified by flash column chromatography on silica gel (10 mg) with 50% ethyl acetate–hexane as eluant to give the *ketone* (**7a**) (32 mg, 45%) as an oil; ν_{max}($CHCl_3$) 3 650m, 3 100–3 600br s, 2 950s, 1 730s, and 1 600m cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.32–4.39 (1 H, m, H_5), 3.35 (3 H, s, OCH_3), 2.27–2.39 (1 H, ddd, *J* 13.6, 9.8, 3.3 Hz, H_{6r}), 2.03–2.25 (4 H, m, H_{3r}, H_{3s}, H_4, and H_7), 1.81–1.88 (1 H, dd, *J* 13.6, 3.6 Hz, H_{6s}), 1.4–1.8 (3 H, m, H_7, H_8, and OH), and 1.36–1.39 (3 H, d, *J* 6.8 Hz, CH_3); *m/z* 184 (M^+, 0.5%), 156 (16), 140 (55), 123 (41), 113 (78), and 100 (100); (Found: C, 65.2; H, 9.0. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.8%).

In addition the alcohols (1R*,2R*,5R*,8S*)- and (1R*,2S*,5R*,8S*)-2,5-*dihydroxy*-1-*methoxy*-8-*methylbicyclo*-[2.2.2]*octane* (**21aa**) and (**21ab**) were isolated from this reaction as a mixture of oils; ν_{max}($CHCl_3$) 3 200s, 2 950m, 1 600s, and 1 100s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.2–4.3 (1 H, m, H_5), 3.7–3.8 (1 H, m, H_2), 3.20 (3 H, s), 2.5–1.3 (8 H, m), and 1.20–1.26 (3 H, CH_3); *m/z* 186 (M^+, 3%), 168 (16), 155 (33),

140 (22), and 100 (100); (Found: M^+ 186.1239. $C_{10}H_{18}O_3$ requires M, 186.1256).

(1R*,8S*)-1-*Methoxy*-8-*methylbicyclo*[2.2.2]*octane*-2,5-*dione* (**18a**).—Alcohol (**7a**) (24 mg, 0.14 mmol) was dissolved in acetone (1 ml) and the solution was cooled to 0 °C. Jones' reagent was added dropwise to the solution until the colour remained permanently orange. Isopropyl alcohol was then added to the solution until it became green. Acetone (5 ml) was added to the mixture which was then filtered through a pad of Celite. The Celite pad was washed with acetone (2 × 5 ml) and the combined organic phases were evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel (1 g) with 30% ethyl acetate–hexane as eluant to give the *ketone* (**18a**) (14 mg, 59%) as an oil; $\nu_{max}(CHCl_3)$ 1 730s and 1 600m cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 3.39 (3 H, s, OCH_3), 2.68–2.77 (1 H, dd, J 17.8, 3.1 Hz, H_{6r}), 2.45–2.52 (1 H, d, J 17.8 Hz, H_{6s}), 2.15–2.55 (5 H, m, H_{3r}, H_{3s}, H_4, H_{7r}, and H_8), 1.46–1.54 (1 H, dd, J 12.7, 5.3 Hz, H_{7s}), and 1.07–1.10 (3 H, d, J 6.6 Hz, CH_3); m/z 182 (M^+ 2%), 156 (18), 139 (88), 111 (84), and 55 (100); (Found: M^+, 182.0955. $C_{10}H_{14}O_3$ requires M, 182.0943).

(4R*,5R*)-4-*Cyanomethyl*-5-*methylcyclohex*-2-*enone* (**22**).—The ketone (**7a**) (18.4 mg, 0.1 mmol) was dissolved in ethanol (0.3 ml) and water (0.6 ml) containing sodium acetate (20 mg, 0.24 mmol) and hydroxylamine hydrochloride (100 mg, 1.45 mmol). The reaction mixture was then stirred under reflux for 2 h after which it was poured into dichloromethane (5 ml). The organic layer was separated, washed with saturated brine, dried (Na_2SO_4), and evaporated to give the oxime (20 mg, 100%).

The crude oxime (20.0 mg) was dissolved in THF (3 ml) at −78 °C containing sodium hydride (10 mg of a 60% suspension in mineral oil). The mixture was stirred for 4 h at −78 °C and then toluene-*p*-sulphonyl chloride (50 mg) was added to it. The mixture was allowed to come to room temperature, and then to stand at room temperature for 72 h under air. Water (2.5 ml) and ethyl acetate (5 ml) were added to the mixture and the layers were then separated. The aqueous layer was extracted with ethyl acetate (3 × 2.5 ml) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residues were purified by chromatography on silica (3 g) with 20% ethyl acetate–hexane (15 ml), then 40% ethyl acetate–hexane (15 ml) then 75% ethyl acetate–hexane (50 ml) as eluant. Three compounds were isolated from this column. In order of elution these were unchanged tosyl chloride, an unknown reaction product (6.3 mg), and the *enone* (**22**) (8.7 mg, 58%) as a colourless oil; $\nu_{max}(CHCl_3)$ 2 950s, 2 240m, 1 680s, and 1 350m cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 6.81–6.86 (1 H, dd, J 12.2, 2.2 Hz, H_3), 6.12–6.17 (1 H, dd, J 12.2, 1.2 Hz), 2.1–2.8 (6 H, m), and 1.13–1.16 (3 H, d, J 6.3 Hz, CH_3); m/z 149 (M^+, 8%), 121 (28), 107 (35), 79 (81), and 68 (100); (Found: M^+ 149.0841. $C_9H_{11}NO$ requires M, 149.0841).

1-(3,5-*Dimethoxyphenyl*)*oct*-1-*ene*.—3,5-Dimethoxybenzaldehyde[21] (15.3 g, 92 mmol) was added to a deep-red solution of the ylide formed by addition of butyl-lithium (100 ml, 1.6M solution in hexane) to heptylphosphonium bromide (72 g) in dry THF (200 ml). The solution was refluxed for 12 h then water was added to discharge the colour. The mixture was extracted with ether (3 × 250 ml) and the combined extracts were dried (Na_2SO_4). The ether was evaporated under reduced pressure, and the residual oil was distilled to give a *cis*- and *trans*-mixture of the *alkene* (21.1 g, 87%) as an oil (b.p. 124–128 °C/0.4 mmHg); $\nu_{max}(CHCl_3)$ 3 000w, 2 960m, 2 940s, 2 850m, 1 605s, 1 595s, 1 210s, and 1 160s cm^{-1}; $\delta_H(CDCl_3$, 80 MHz) 7.25–7.34 (1 H, m, ArC*H*=CH), 6.18–6.51 (3 H, m, Ar–H), 5.49–5.85 (1 H, dt, J 8, 13 Hz, ArCH=C*H*), 3.79 (6 H, s, OCH_3), 2.07–2.37, (2 H, m, CH=CHCH_2), 1.13–1.52 [8 H, m, $(CH_2)_4$], and 0.76–0.94 (3 H, m, CH_2CH_3); m/z 248 (M^+, 78), 219 (2), 205 (14), 191 (100), 167 (54), and 152 (94); (Found: C, 77.3; H, 9.6. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%).

1-(3,5-*Dimethoxyphenyl*)*octane* (**11b**).—1-(3,5-Dimethoxyphenyl)oct-1-ene (10.0 g, 40 mmol) was dissolved in a suspension of palladium on charcoal (1 g, 5%) in ethyl acetate–methanol (250 ml, 1:1 mixture) and the resulting mixture was stirred under a hydrogen atmosphere at room temperature for 24 h. The brown-red suspension was filtered through a Celite pad, and the residues were washed with ethyl acetate. The combined organic phases were evaporated under reduced pressue, and the residues were distilled to give the *alkane* (**11b**) (8.4 g, 83%) as an oil, b.p. 142–144 °C/0.2 mmHg; $\nu_{max}(CHCl_3)$ 2 940s, 2 860s, 1 605s, 1 595s, 1 460s, and 1 155s cm^{-1}; $\delta_H(CDCl_3$, 80 MHz) 6.33–6.36 (2 H, d, J 2 Hz, ArH), 6.27–6.31 (1 H, t, J 2 Hz, ArH), 3.77 (6 H, s, OCH_3), 2.45–2.63 (2 H, t, J 8 Hz, ArCH_2), 1.28–1.58 [12 H, m, $(CH_2)_6$], and 0.80–0.94 (3 H, t, J 6 Hz, CH_2CH_3); m/z 250 (M^+, 29), 208 (2), 184 (4), 167 (15), 152 (100), and 121 (4); (Found: C, 76.8; H, 10.4. $C_{16}H_{26}O_2$ requires C, 76.8; H, 10.5%).

1,4-*Dimethoxy*-3-*octylhexa*-1,4-*diene* (**12b**).—1-(3,5-Dimethoxyphenyl)octane (7.2 g, 8.8 mmol) was dissolved in a mixture of ethanol (30 ml) and liquid ammonia (100 ml) at −78 °C. Dry THF (20 ml) was added to the solution, which was then allowed to come to the boil. Lithium (1.8 g) was added to the stirred solution in 0.05 g pieces. After all the lithium had been added the ammonia was allowed to evaporate under a stream of nitrogen. Saturated aqueous ammonium chloride was added to neutralise the residues, and the resulting solution was extracted with dichloromethane (4 × 50 ml). The combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the diene (**12b**) as an oil which was purified by distillation to give *compound* (**12b**) as a colourless oil (6.3 g, 86%), b.p. 75–76 °C/0.2 mmHg; $\nu_{max}(CHCl_3)$ 2 920s, 1 695s, 1 670s, 1 395s, and 1 140s cm^{-1}; $\delta_H(CDCl_3$, 90 MHz) 4.6 (2 H, d, J 4 Hz, C*H*=COMe), 3.6 (6 H, s, CH_3), 2.6–3.1 (3 H, m, C*H*C=CCH_2), 1.2–1.4 [14 H, br s, $(CH_2)_7$], and 0.9 (3 H, t, J 7 Hz, CH_2CH_3); m/z 221 (M^+, 1.5%), 152 (28), 139 (100), and 109 (30); (Found: C, 76.3; H, 11.3. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%).

(1R*,2R*,8S*)-, (1R*,2S*,8S*)-, *and* (1R*,2S*,8R*)-2-*Chloro*-1-*methoxy*-8-*octyl*-5-*oxobicyclo*[2.2.2]*octane*-2-*carbonitrile* (**5cx**), (**5cy**), *and* (**5dx**).—The diene (**12b**) (6.0 g, 24 mmol) was mixed with 2-chloroacrylonitrile (20 ml) and the solution was heated at 65 °C for 8 h. It was then allowed to cool after which it was poured into a mixture of THF and 3M hydrochloric acid (400 ml of a 1:1 mixture). This two-phase mixture was vigorously stirred at room temperature for 40 h and the aqueous and organic layers were then separated. The aqueous layer was extracted with ethyl acetate (3 × 200 ml) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oily residue. This was purified by flash column chromatography on silica gel (250 g) with 50% dichloromethane–light petroleum (b.p. 40–60 °C) (2 l), then 75% dichloromethane–light petroleum (1 l), then dichloromethane (1 l) as eluant to give the ketone (**5cx**) (2.0 g, 26%) as an oil, free of stereoisomers; in total 3.9 g (51%) of the adducts (**5cx**), (**5cy**), and (**5dx**) in a 15:5:1 ratio. In addition the rearranged compounds (**13c**), (1*R**,4*R**)- and (1*R**,4*S**)-4-octyl-2,6-dioxobicyclo[3.2.1]octane-1-carbonitrile were obtained (0.56 g, 9%).

For *ketone* (**5cx**); $\nu_{max}(CHCl_3)$ 2 850s, 1 725s, and 1 600m cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 3.42 (3 H, s, OCH_3), 2.88–2.95 (1 H, dd, *J* 15.5, 3.2 Hz, H_{3s}), 2.77–2.86 (1 H, dd, *J* 18.7, 3.6 Hz, H_{6r}), 2.48–2.55 (1 H, dd, *J* 15.5, 2.7 Hz, H_{3r}), 2.46–2.51 (1 H, d, *J* 18.7 Hz, H_{6s}), 2.20–2.30 (3 H, m, H_4, H_{7r}, H_8), 1.60–1.69 (1 H, dd, *J* 13.8, 5.8 Hz, H_{7s}), 1.24–1.30 [14 H, m, $(CH_2)_7$], and 0.84–0.90 (3 H, t, *J* 6.5 Hz, CH_3); *m/z* 325 (M^+, 3%), 290 (5), 212 (48), 176 (23), 125 (85), and 97 (100); (Found: M^+, 325.1802. $C_{18}H_{28}ClNO_2$ requires *M*, 325.1809).

For *diketones* (**13c**); $\nu_{max}(CHCl_3)$ 1 750s and 1 730s cm^{-1}; $\delta_H(CDCl_3, 250\ MHz)$ 2.0–2.8 (bicyclic protons), 1.24–1.30 [14 H, $(CH_2)_7$], and 0.84–0.98 (3 H, t, *J* 6.7 Hz, CH_3); *m/z* 275 (M^+, 3%), 213 (12), and 167 (100); (Found: M^+, 275.1868. C, 73.6; H, 9.1; N, 5.0. $C_{17}H_{25}NO_2$ requires *M*, 275.1885. C, 74.2; H, 9.1; N, 5.1%).

1-*Hydroxymethyl*-3,5-*dimethoxyhexa*-2,5-*diene* (**12c**).—3,5-Dimethoxycyclohexa-2,5-dienecarboxylic acid (70.0 g, 0.38 mol) was reduced in dry ether (400 ml) with lithium aluminium hydride (33.6 g) in dry ether (200 ml) according to the method of Chapman and Fitton.[18] The required alcohol (**12c**) (51.1 g, 79%) was obtained as an oil which solidified with time, b.p. 120–123 °C/0.5 mmHg, m.p. 46–47 °C (lit.,[18] m.p. 38–40 °C); $\nu_{max}(CHCl_3)$ 3 500br, 3 000w, 1 690s, 1 660s, 1 400s, and 1 140s cm^{-1}; $\delta_H(CDCl_3, 80\ MHz)$ 4.56–4.63 (2 H, dt, *J* 4, 1 Hz, C*H*=COCH$_3$), 3.56 (6 H, s, OCH_3), 3.37–3.49 (2 H, d, *J* 4 Hz, CH_2OH), 3.1–3.3 (1 H, m, C*H*CH$_2$OH), 2.81–2.85 (1 H, dt, *J* 6, 1 Hz, C*H*H), and 2.72–2.76 (1 H, dt, *J* 6, 1 Hz, CH*H*); *m/z* (CI) 170 (M^+, 0.5%), 168 (5), 139 (100), 124 (11), 109 (10), and 96 (7); (Found: C, 63.4; H, 8.4. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%).

3,5-*Dimethoxycyclohexa*-2,5-*dienecarboxylic Acid*.—3,4,5-Trimethoxybenzoic acid (80 g, 370 mmol) was reduced by a modification of the method of Kuehne and Lambert.[17] It was dissolved in methanol (480 ml) and the solution was cooled in a solid CO_2–acetone bath, under a solid CO_2–acetone condenser. Dry ammonia (1.6 l) was condensed into this solution, and lithium (48.0 g) was added in 1 g portions to the resulting mixture. After addition was completed, ammonium chloride (200 g) was added and the liquid ammonia was allowed to evaporate under a stream of nitrogen. Ice-cold water was added to the residue until it dissolved, and this solution was placed in an ice–salt–water bath maintained at 0 °C. 2M Hydrochloric acid was added to the solution until it became acidic to Congo Red, when white crystals precipitated out. The mixture was poured onto dichloromethane (1.5 l) and the mixture was shaken. The organic phase was run-off, and the aqueous phase was re-acidified and re-extracted. This process was repeated until extraction did not cause neutralisation of the aqueous phase. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the required acid (69.0 g, 99%) as a white solid mass, m.p. 100–107 °C. Recrystallisation from ether–pentane gave prisms, m.p. 106–107 °C (lit.,[17] 105 °C); $\nu_{max}(CHCl_3)$ 3 500–2 500br s, 1 710s, 1 660s, 1 610s, 1 400s, and 1 160s cm^{-1}; $\delta_H(CD_3SOCD_3, 80\ MHz)$ 4.73–4.81 (2 H, dt, *J* 1.2, 3.7 Hz, C*H*=COMe), 3.84–3.92 (1 H, t, *J* 3.7 Hz, C*H*CO$_2$H), 3.52 (6 H, s, OCH_3), 2.62–2.73 (1 H, dt, *J* 1.2, 7 Hz, HC*H*), 2.45–2.57 (1 H, m, obscured by solvent residual peaks, *H*CH); *m/z* (CI) 184 (M^+, 4%), 182 (17), 170 (21), 139 (44), 125 (100), 98 (88), and 68 (91); (Found: C, 57.6; H, 6.7. $C_9H_{12}O_4$ requires C, 57.4; H, 6.6%).

3,5-*Dimethoxycyclohexa*-2,4-*dienylmethyl t-Butyldimethylsilyl Ether* (**12d**).—The alcohol (**12c**) (2.0 g, 12 mmol) was dissolved in dry DMF (3 ml) with imidazole (2.0 g) and t-butyldimethylsilyl chloride (2.15 g) was added to the solution. The black mixture was stirred at room temperature for 15 h, after which the reaction was quenched by addition of pentane (15 ml) and water (10 ml). The two phases were separated and the aqueous phase was extracted with pentane (2 × 25 ml). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a heavy oil (4.0 g). This was purified by bulb-to-bulb distillation to give the *ether* (**12d**) (3.36 g, 100%) as a colourless oil, b.p. 180 °C (oven temp.)/0.35 mmHg; $\nu_{max}(CHCl_3)$ 2 950s, 1 690s, 1 660s, 1 140s, and 840s cm^{-1}; $\delta_H(CDCl_3, 90\ MHz)$ 4.55 (2 H, d, *J* 4 Hz, C*H*=COCH$_3$), 3.52 (6 H, s, OCH_3), 3.35–3.42 (2 H, d, *J* 6 Hz, CH_2OSi), 2.9–3.2 (1 H, m, C*H*CH$_2$), 2.65–2.75 (2 H, m, CH_2), 0.85 [9 H, s, C(CH_3)$_3$], 0.01 [6 H, s, Si(CH_3)$_2$]; *m/z* (CI) 285 ([M + H]$^+$, 10%), 271 (100), 255 (6), 213 (8), and 194 (2); (Found: C, 63.3; H, 10.0. $C_{15}H_{28}SiO_3$ requires C, 63.4; H, 9.9%).

Allyl 3,5-*Dimethylcyclohexa*-2,4-*dienylmethyl Ether* (**12e**).—The alcohol (**12c**) (1.70 g, 10 mmol) was dissolved in dry THF (10 ml) and the solution was added dropwise to a suspension of sodium hydride (0.46 g of a 50% suspension in mineral oil). The solution was cooled to 0 °C and allyl bromide (2.16 ml) was added. The mixture was then refluxed for 24 h before removal of the solvent under reduced pressure. The residue was dissolved in ethyl acetate (100 ml), and the solution formed was filtered, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was purified by distillation to give the *ether* (**12e**) (1.94 g, 92%) as an oil, b.p. 95–97 °C/0.3 mmHg; $\nu_{max}(CHCl_3)$ 2 950s, 2 850s, 1 690s, 1 660s, 1 600m, 1 440s, 1 400s, 1 100–1 200s, and 915s cm^{-1}; $\delta_H(CDCl_3, 90\ MHz)$ 5.87–6.20 (1 H, ddt, *J* 13, 10, 5 Hz, C*H*=CH$_2$), 5.26–5.41 (1 H, dt, *J* 13, 1 Hz, CH=C*H*H *trans*), 5.16–5.27 (1 H, dt, *J* 10, 1 Hz, CH=CH*H cis*), 4.72 (2 H, br s, C*H*=COCH$_3$), 4.03–4.13 (2 H, dt, *J* 5, 1 Hz, OCH_2CH=), 3.66 (6 H, s, OCH_3), 3.32 (2 H, br s, CHCH_2O), 3.10–3.30 (1 H, m, C*H*CH$_2$O), and 2.73–2.89 (2 H, m, CH_2); *m/z* 167 (M^+ − C_3H_5 − H_2, 7%), 149 (9), 139 (100), 127 (58), 109 (34), and 95 (17); (Found: C, 68.7; H, 8.9. $C_{12}H_{18}O_3$ requires C, 68.5; H, 8.6%).

3,5-*Dimethoxycyclohexa*-2,4-*dienylmethyl Diphenyl-t-butylsilyl Ether* (**12f**).—The alcohol (**12c**) (1.02 g, 6 mmol) was dissolved in dry DMF (25 ml), and imidazole (1.98 g), and diphenyl-t-butylsilyl chloride (1.72 ml) were added to the solution. The mixture was stirred at room temperature for 20 h after which the reaction was then quenched by adding water (50 ml) and pentane (50 ml). The layers were separated and the aqueous phase was extracted with pentane (3 × 50 ml). The combined organic phases were dried (K_2CO_3), filtered, and evaporated under reduced pressure to give an oil. This was purified by bulb-to-bulb distillation to give the *ether* (**12f**) (2.50 g, 96%) as an oil, b.p. 200–202 °C/0.2 mmHg; $\nu_{max}(CHCl_3)$ 2 950s, 2 865s, 1 690s, 1 660s, 1 605m, 1 590m, 1 470s, 1 400s, 1 155s, 1 115s, and 700s cm^{-1}; $\delta_H(CDCl_3, 80\ MHz)$ 7.29–7.79 (10 H, m, Ar*H*), 4.68–4.75 (2 H, dt, *J* 3, 1 Hz), 3.55 (6 H, s, OCH_3), 3.51 (2 H, d, *J* 6 Hz, CHCH_2OSi), 3.05–3.20 (1 H, br m, C*H*CH$_2$OSi), 2.80–2.82 (1 H, dt, *J* 6, 1 Hz, *H*CH), 2.71–2.75 (1 H, dt, *J* 6, 1 Hz, HC*H*), and 1.08 [9 H, s, C(CH_3)$_3$]; *m/z* 256 (1), 239 (1), 200 (19), and 199 (100); (Found: C, 73.2; H, 7.7. $C_{25}H_{32}O_3Si$ requires C, 73.5; H, 7.9%).

(1R*,4R*)- *and* (1R*,4S*)-4-*Hydroxymethyl*-2,6-*dioxobicyclo*[3.2.1]*octane*-1-*carbonitrile* (**13d**), (1R*,2R*,8S*) *and* (1R*,2S*,8S*)-2-*Chloro*-8-*hydroxymethyl*-1-*methoxy*-5-*oxobicyclo*[2.2.2]*octane*-2-*carbonitrile* (**5ex**) *and* (**5ey**), *and* (1R*,3R*,6S*,7R*)-3-*Methoxy*-9-*oxo*-4-*oxatricyclo*[4.2.2.0^{3,7}]*decane*-1-*carbonitrile* (**23**).—The diene (**12d**) (1.46 g, 5.1 mmol) and 2-chloroacrylonitrile (3.5 ml) were heated together at 90 °C for 90 min. The remaining dienophile was evaporated under reduced pressure and the oily residue dissolved in a mixture of THF, water, and acetic acid (3:2:2; 49 ml) was heated at 80 °C for 18 h. The solution was then poured onto brine (50 ml) and

the mixture was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with brine (50 ml) dried ($MgSO_4$), and evaporated under reduced pressure to give a gum (1.46 g). This was purified by flash column chromatography on silica gel (200 g) with ethyl acetate–hexane (2 l) then 75% ethyl acetate–hexane (2 l) as eluant to give, in order of elution; the acetal (**23**) (0.044 g, 4%) as a colourless oil, the ketone (**5ex**) (0.301 g, 24%) as a microcrystalline mass m.p. 57.5–59 °C; the ketone (**5ey**) (0.033 g, 3%); and the diketones (**13d**) (0.080 g, 8%) as a mixture of epimers.

For the *acetal* (**23**); $\nu_{max}(CHCl_3)$ 2 950s, 2 830m, 2 240m, 1 730s, 1 600m, 1 100s, and 985s cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 3.88–3.95 (1 H, ddd, *J* 8.9, 3.6, 0.6 Hz, H_{9r}), 3.59–3.63 (1 H, d, *J* 8.9 Hz, H_{9s}), 3.31 (3 H, s, OCH_3), 2.76–2.94 (2 H, m, H_{3r} and H_{3s}), and 2.25–2.41 (6 H, m); *m/z* (CI) 225 ($[M + NH_4]^+$, 100%), 198 (6), 181 (4), and 99 (7); (Found: M^+, 207.0878. $C_{11}H_{13}NO_3$ requires *M*, 207.0896).

For the *ketone* (**5ex**); $\nu_{max}(CHCl_3)$ 3 100–3 500br, 2 950m, 1 730s, 1 600m, and 1 220s cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 3.7–3.5 (2 H, m, CH_2OH), 3.42 (3 H, s, OCH_3), 2.91–2.98 (1 H, dd, *J* 16.7, 2.5 Hz, H_{3s}), 2.76–2.84 (1 H, dd, *J* 15.8, 2.8 Hz, H_{6r}), 2.55–2.65 (1 H, d, *J* 16.7 Hz), 2.1–2.5 (4 H, m), 1.8 (1 H br, OH), and 1.65–1.75 (1 H, ddd, *J* 10.4, 6.4, 3.2 Hz, H_{7r}); *m/z* 243 (9), 212 (25), 156 (21), and 125 (100); (Found: C, 54.1; H, 6.1; N, 5.5. $C_{11}H_{14}ClNO_3$ requires C, 54.2; H, 5.8; N, 5.8%).

For the *ketone* (**5ey**); $\nu_{max}(CHCl_3)$ 3 100–3 600br, 2 850s, 2 250m, 1 730s, 1 110s, and 1 090s cm^{-1}; $\delta_H(CDCl_3$, 400 MHz) 4.02–4.06 (1 H, dd, *J* 10, 3 Hz), H_9), 3.64–3.68 (1 H, d, *J* 10 Hz, H_9), 3.44 (3 H, s, OCH_3) 2.3–3.0 (7 H, m), and 1.5 (1 H, br, OH); *m/z* 244 ($[M + H]^+$, 18%), 212 (16), 179 (9), 156 (10), 125 (50), and (85).

For the *diketones* (**13d**); $\nu_{max}(CHCl_3)$, 3 580s, 3 100–3 600br, 2 920s, 2 230m, 1 740s, 1 730s, and 1 600m cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 3.98–4.03 (1 H, dd, *J* 9.9, 2.8 Hz, H_9), 3.60–3.63 (1 H, d, *J* 9.9 Hz, H_9), 2.70–2.85 (2 H, m, $H_{3r,s}$), 2.30–2.60 (5 H, m), and 1.7 (1 H, br s, OH).

8-*Allyloxymethyl*-2-*chloro*-1-*methoxybicyclo*[2.2.2]*octane*-2-*carbonitrile* (**5gx**), (**5gy**), (**5hx**), *and* (1R*,4R*)- *and* (1R*,4S*)-4-*Allyloxymethyl*-2,6-*dioxobicyclo*[3.2.1]*octane*-1-*carbonitrile* (**13e**) *and* (**13f**).—The diene (**12e**) (0.82 g) and 2-chloroacrylonitrile (3 ml) were heated together at 65 °C for 3 h. The solution was then allowed to cool and the residual dienophile was evaporated under reduced pressure. The oily liquid that remained was dissolved in a mixture of THF and 2M hydrochloric acid (1:1 mixture; 25 ml) and the resulting two-phase mixture was stirred vigorously at room temperature for 24 h. The two phases were then separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel (100 g) with 30% ethyl acetate–hexane (500 ml) then 50% ethyl acetate–hexane (500 ml) then 75% ethyl acetate–hexane (1 l) as eluant. The ketones (**5gx**), (**5gy**), and (**5hx**) were the first eluted compounds, obtained as an oil (0.31 g, 27%) in a 9:1:2 ratio. The major isomer, tentatively assigned the structure (**5gx**) was readily separated from this mixture. The diketones (**13e**) and (**13f**) were also obtained as a solid (0.25 g, 28%) in a 3:1 ratio. The major isomer (**13e**) could be separated from this mixture by recrystallisation from carbon tetrachloride, which gave prisms, m.p. 81–82.5 °C.

For *ketone* (**5gx**); $\nu_{max}(CHCl_3)$ 2 930s, 2 850s, 1 740s, 1 600m, and 1 110s cm^{-1};[1] $\delta_H(CDCl_3$, 250 MHz) 5.77–5.88 (1 H, m, $H_{2'}$), 5.16–5.25 (2 H, m, 2 × $H_{3'}$), 3.91–3.93 (2 H, d, *J* 5.3 Hz, 2 × $H_{1'}$), 3.42 (3 H, s, OCH_3), 3.26–3.36 (2 H, m, 2 × H_9), 2.90–2.97 (1 H, dd, *J* 15.4, 3.7 Hz, H_3), 2.74–2.82 (1 H, dd, *J* 18.4, 2.4 Hz, H_6), 2.57–2.65 (1 H, d, *J* 18.4 Hz, H_6), and 1.98–2.66 (5 H, m); *m/z* 283 (M^+, 1%), 248 (1), and 125 (100); (Found: C, 59.7; H, 6.7; N, 4.9; M^+, 283.0977. $C_{14}H_{18}ClNO_3$ requires C, 59.2; H, 6.4; N, 5.2%; *M*, 283.0975).

For the *diketone* (**13e**); $\nu_{max}(CHCl_3)$, 2 940s, 2 850s, 2 250m, 1 750s, 1 730s, 1 600s, and 1 110s cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 5.79–5.94 (1 H, ddd, *J* 17.3, 13.1, 5.7 Hz, H_2), 5.22–5.29 (1 H, dd, *J* 17.3, 1.6 Hz, H_3), 5.17–5.22 (1 H, dd, *J* 13.1, 1.1 Hz, H_3), 3.90–4.04 (2 H, m, 2 × H_1), 3.36–3.43 (1 H, dd, *J* 9.4, 7.9 Hz, H_9), 3.24–3.30 (1 H, dd, *J* 7.9, 5.6 Hz, H_9), and 2.0–3.0 (8 H, m protons of bicycle); *m/z* 233 (M^+, 0.6%), 205 (13), 176 (55), 148 (51), 134 (39), 125 (81), and 79 (100); (Found: C, 67.0; H, 6.5; N, 5.9%. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%).

(1R*,2R*,5R*,8S*)-2-*Chloro*-5-*hydroxy*-8-*hydroxymethyl*-1-*methoxybicyclo*[2.2.2]*octane*-2-*carbonitrile* (**6ex**).—The ketone (**5cx**) (0.040 g, 0.16 mmol) was dissolved in methanol (3 ml) and the solution was cooled to 0 °C. Sodium borohydride (0.006 g) was added to the solution, which then was stirred at room temperature for 90 min. A further portion of reducing agent (0.006 g) was added and the solution was stirred for a further 90 min. Ammonium chloride (50 mg) was added to the solution and the solvent was evaporated under reduced pressure. The solid residue was partitioned between water (5 ml) and ethyl acetate (5 ml) and the aqueous phase was extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue. This was purified by preparative TLC on silica with ethyl acetate as eluant to give the *diol* (**6ex**) (0.033 g, 82%) as prisms; m.p. 74–75 °C; $\nu_{max}(CHCl_3)$ 3 200–3 600br, 2 935s, 1 440m, 1 315m, and 1 115s cm^{-1}; $\delta_H(CDCl_3$, 250 MHz) 4.09–4.20 (1 H, ddd, *J* 10.4, 7.2, 1.7 Hz, H_5), 3.66–3.78 (2 H, m, CH_2OH), 3.37 (3 H, s, OCH_3), 2.68–2.75 (1 H, dd, *J* 15.3, 3.2 Hz, H_{3s}), 2.51–2.40 (1 H, td, *J* 10.4, 3.0 Hz, H_{6r}), 2.37–2.44 (1 H, dd, *J* 15.3, 3.0 Hz, H_{3r}), 2.15–2.25 (1 H, m, H_8), 2.15–2.20 (1 H, dd, *J* 10.4, 7.2 Hz, H_{6s}), 1.95–2.05 (1 H, ddd, *J* 13.7, 5.9, 3.2 Hz, H_{7r}), 1.90–1.95 (1 H, m, H_4), 1.72–1.80 (1 H, dd, *J* 13.7, 4.8 Hz, H_{7s}), and 2.5–3.0 (2 H, br, 2 × OH); *m/z* 227 ($M^+ - H_2O$, 2%), 214 (22), 140 (79), and 109 (100); (Found: C, 54.4; H, 6.5; N, 5.8. $C_{11}H_{16}ClNO_3$ requires C, 53.8; H, 6.6; N, 5.8%).

(1R*,9R*)- *and* (1R*,9S*)-9-*Chloro*-1,6-*dimethoxy*-5-*oxatricyclo*[4.3.1.$0^{3,7}$]*decane*-9-*carbonitrile* (**24**).—The diene (**12f**) (2.30 g) was heated in dry toluene (5 ml) with 2-chloroacrylonitrile (5 ml) for 5 h at 65 °C. The solution was then allowed to cool to room temperature and the solvent and residual dienophile were then evaporated off under reduced pressure. The residual gum containing the crude mixture of adducts (**5ix**) and (**5iy**) was dissolved in dry THF (75 ml) and this solution was cooled to 0 °C. *Tetra*butylammonium fluoride (6 ml of a 1M solution in THF) was added dropwise to the cooled solution, which was then stirred at 0 °C for 5 h. Toluene-*p*-sulphonic acid (0.5 g) was then added to the solution, which was allowed to warm up and which was then stirred at room temperature for 18 h. The solution was then neutralised by addition of solid sodium carbonate and the solvent was evaporated under reduced pressure. The residue was then partitioned between water (50 ml) and ethyl acetate (50 ml) and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (50 ml), and brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The oily residues were purified by flash column chromatography on silica (150 g) with 20% ethyl acetate–hexane as eluant. The major compounds isolated were the epimeric mixture of *acetals* (**24**) which were recrystallised from carbon tetrachloride–hexane to give prisms, m.p. 106–107 °C, (0.96 g, 48%); $\nu_{max}(CHCl_3)$ 2 900m, 1 600w, and

1 100s cm^{-1}; δ_H($CDCl_3$, 250 MHz). (Major isomer) 3.91–3.96 (1 H, dd, *J* 7.8, 3.1 Hz, H_4), 3.62–3.65 (1 H, d, *J* 7.8 Hz, H_4), 3.37 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 2.86–2.93 (1 H, dd, *J* 15.9, 3.7 Hz, H_8), 2.45–2.52 (1 H, dd, *J* 15.9, 2.2 Hz, H_8), 2.28–2.57 (3 H, m, 2 × H_2, H_3), 2.09–2.15 (1 H, d, *J* 13.8 Hz, H_{10}), 2.06–2.10 (1 H, m, H_7), and 1.90–1.96 (1 H, dd, *J* 13.8, 1.2 Hz, H_{10}); *m/z* 257 (M^+, 0.6%), 242 (1), 192 (8), and 99 (100); (Found: C, 56.0; H, 6.2; N, 5.3. $C_{12}H_{16}ClNO_3$ requires C, 55.9; H, 6.3; N, 5.4%).

6-Methoxy-4-methyl-2,3,4,7-tetrahydrobenzofuran (**10**).—6-Methoxy-4-methyl-2,3-dihydrofuran[6] (1.0 g, 6.1 mmol) was dissolved in THF (5 ml) and the solution was added to a mixture of ethanol (5 ml) and liquid ammonia (25 ml) at −78 °C. The resulting mixture was allowed to come to reflux, and lithium shot (1.6 g) was added to it over a 3 h period. The ammonia was evaporated under a stream of nitrogen and saturated ammonium chloride solution (5 ml) was added to the white residues. These were then extracted with ether (3 × 30 ml) and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (25 ml) and brine (25 ml), and dried (Na_2SO_4). The organic layer was filtered, and evaporated under reduced pressure to give an oil which was purified by Kugelrohr distillation to give *diene* (**10**) (0.89 g, 86%) as a colourless liquid, b.p. 79–80 °C/0.1 mmHg; ν_{max}($CHCl_3$) 2 950s, 1 720s, 1 660s, 1 450s, 1 390s, 1 160s, 1 090s, and 980s, cm^{-1}; δ_H($CDCl_3$, 90 MHz) 4.64 (1 H, d, *J* 3 Hz, H_5), 4.23–4.44 (2 H, t, *J* 9 Hz, H_2), 3.57 (3 H, s, OCH_3), 2.2–3.1 (5 H, m, H_3, H_4, H_7), and 1.0–1.1 (3 H, d, *J* 6 Hz, $CHCH_3$); *m/z* 166 (M^+, 28%), 164 (26), 151 (100), 135 (45), and 91 (50); (Found: C, 72.3; H, 8.3. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%).

2-Chloro-4-(2′-hydroxyethyl)-1-methoxy-8-methyl-5-oxobicyclo[2.2.2]*octane-2-carbonitrile* (**25**) *and 5-(2′-Hydroxyethyl)-2,6-dioxobicyclo*[3.2.1]*octane-1-carbonitrile* (**26**).—The diene (**10**) (0.83 g) and 2-chloroacrylonitrile (5 ml) were heated together at 65 °C for 8 h. The solution was then allowed to cool to room temperature and the oily residue was dissolved in a 1:1 mixture of THF and 2M hydrochloric acid (25 ml). This mixture was stirred at room temperature for 24 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 ml) and the combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The oily residue was purified by chromatography on silica (25 g) with 30% ethyl acetate–hexane (50 ml) then 40% ethyl acetate–hexane (50 ml) then 75% ethyl acetate–hexane (250 ml) as eluant. The ketones (**25**) and the dione (**26**) were obtained as a 2:3 mixture from which the pure dione (**26**) could be obtained by fractional recrystallisation from dichloromethane–pentane (0.091 g, 8%) as prisms, m.p. 177–178 °C. The mother liquor contained the unique ketone (**25**), contaminated by the dione (**26**) (0.15 g combined).

For the *dione* (**26**); ν_{max}($CDCl_3$) 3 300s, 1 720s, and 1 600m cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.11–4.26 (2 H, m, 2 × H'_2), 3.06–3.16 (1 H, dd, *J* 16.3, 8.2 Hz, H_3), 2.81–2.87 (1 H, d, *J* 15.2 Hz, H_7), 2.3–2.4 (1 H, m, H_4), 2.34–2.40 (1 H, d, *J* 15 Hz), 2.3 (2 H, m, 2 × H_8), 2.17–2.23 (1 H, d, *J* 16.3 Hz, H_3), 1.9–2.0 (2 H, m, 2 × H'_1), 1.02–1.05 (3 H, d, *J* 7.2 Hz, CH_3); *m/z* 221 (M^+, 11%), 203 (8), 193 (9), 175 (47), 162 (56), and 69 (100); (Found: C, 65.4; H, 6.8; N, 6.3. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%).

For the *ketone* (**25**); ν_{max}($CHCl_3$) 3 600s, 1 730s, 1 600m, and 1 100s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 3.6–3.7 (2 H, m, 2 × H_2), 3.4 (3 H, s, OCH_3), 2.0–3.0 (8 H, m), 1.60–1.68 (1 H, dd, *J* 5.9, 14.5 Hz, H_8), and 0.82–0.85 (3 H, d, *J* 6.7 Hz, CH_3); *m/z* 254 (M^+ − OH, 1%), 238 (4), 184 (26), 162 (33), 143 (41), 111 (97), 91 (100), 81 (97), and 77 (99).

(1R*,2R*,5R*,8S*)-*2-Chloro-5-hydroxy-1-methoxy-8-octylbicyclo*[2.2.2]*octane-2-carbonitrile* (**6cx**).—The ketone (**5cx**) (51 mg, 0.16 mmol) was dissolved in THF (5 ml) and the solution was added dropwise to a suspension of lithium tri-t-butoxyaluminium hydride (160 mg) in THF (5 ml) at −78 °C. The mixture was stirred and allowed to come to room temperature overnight. Water was slowly added to the white suspension until two layers of equal volume had formed. These were then separated and the aqueous phase was extracted with ether (3 × 5 ml). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give an oil. This was purified by flash chromatography on silica gel (5 g) with 75% dichloromethane–pentane as eluant to give the *alcohol* (**6cx**) (50 mg, 97%) as an oil, which solidified on standing to give needles, m.p. 45.5–47 °C; ν_{max}($CHCl_3$) 3 600m, 2 920s, 2 850s, 2 230w, 1 600w, 1 410m, and 1 120s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.21–4.28 (1 H, dddd, *J* 9.7, 4.6, 2.8, 1.5 Hz, H_5), 3.37 (3 H, s, OCH_3), 2.64–2.71 (1 H, dd, *J* 15.1, 3.7 Hz, H_{3s}), 2.33–2.44 (1 H, ddd, *J* 13.6, 9.7, 3.7 Hz, H_6), 2.18–2.26 (1 H, dd, *J* 15.1, 2.6 Hz, H_{3r}), 2.12–2.23 (1 H, m, H_6), 1.89–2.03 (1 H, m, H_4), 1.73–1.81 (1 H, dd, *J* 12.8, 6.7 Hz, H_7), 1.70–1.77 (1 H, dd, *J* 13.7, 3.7 Hz, H_6), 1.61–1.69 (1 H, m, H_8), 1.49–1.75 (1 H, br s, OH), 1.26 [14 H, br s, $(CH_2)_7$], and 0.84–0.90 (3 H, t, *J* 6.6 Hz, CH_3); *m/z* 327 (M^+, 1%), 309 (2), 216 (35), 214 (100), and 100 (99); (Found: M^+, 327.1994. $C_{18}H_{30}ClNO_2$ requires *M*, 327.1965).

(1R*,5R*,8S*)-*5-Hydroxy-1-methoxy-8-octylbicyclo*[2.2.2]*octan-2-one* (**7b**).—The chloronitrile (**6cx**) (0.458 g, 1.4 mmol), sodium sulphide nonahydrate (0.350 g) and potassium hydroxide (0.240 g) were dissolved in ethanol and the solution was heated under reflux for 26 h. The solution was then allowed to cool and the solvent was removed under reduced pressure. The residue was partitioned between water (25 ml) and ethyl acetate (25 ml) and the aqueous phase was extracted with ethyl acetate (2 × 25 ml). The aqueous layer was then acidified with 2M hydrochloric acid and was extracted with ethyl acetate (2 × 25 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate (25 ml) and brine (25 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give an oil. This was purified by flash column chromatography on silica gel (25 g) with dichloromethane as eluant to give the *ketone* (**7b**) as the second eluted compound (0.084 g, 21%); ν_{max}($CHCl_3$) 3 650w, 2 920s, 2 810s, 1 730s, 1 600m, and 895s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.28–4.38 (1 H, m, H_5), 2.29–2.39 (1 H, ddd, *J* 13.5, 9.8, 2.6 Hz, H_{6r}), 2.03–2.25 (4 H, m, H_{3r}, H_{3s}, H_4, and H_7), 1.73–1.85 (1 H, dd, *J* 13.6 Hz, 3.6 Hz, H_{6s}), 1.4–1.8 (3 H, m, H_7, H_8, and OH), 1.25–1.30 [14 H, s, $(CH_2)_7$], and 0.84–0.89 (3 H, t, *J* 6.5 Hz, CH_3); *m/z* 282 (M^+, 0.7%), 238 (12), 209 (13), 180 (16), 141 (100), 113 (93), and 100 (58); (Found: M^+, 282.2198. $C_{17}H_{30}O_3$ requires *M*, 282.2195).

In addition the *diols* (**21ba**) and (**21bb**) were isolated from this reaction (40 mg, 10%). For spectral details see the following experiment.

(1R*,2R*,5R*,8S*)- *and* (1R*,2S*,5R*,8S*)-*2,5-Dihydroxy-1-methoxy-8-octylbicyclo*[2.2.2]*octane* (**21ba**) *and* (**21bb**).—The ketone (**7b**) (8.0 mg) was dissolved in methanol (0.5 ml) and sodium borohydride (10 mg) was added to this solution. The mixture was stirred at room temperature for 2 h then 2M hydrochloric acid (0.10 ml) was added to it. The mixture was evaporated to dryness and the residue was purified by chromatography on silica gel (0.5 g) with 50% ethyl acetate–hexane as the eluant. The mixture of *diols* (**21ba**) and (**21bb**) (8.0 mg, 100%) was obtained as an oil. This mixture was identical in TLC properties and ^1H NMR with the lower running compounds isolated from hydrolysis of the chloronitrile (**6cx**); ν_{max}($CHCl_3$) 3 500s, 1 600m, and 1 100s cm^{-1}; δ_H($CDCl_3$, 250 MHz) 4.1–4.3 (1 H, m, H_5), 3.6–3.8 (1 H, m, H_2),

3.20 (3 H, s, OCH_3), 1.3–2.2 (8 H, m), 1.2–1.3 [14 H, br s, $(CH_2)_7$], and 0.84–0.89 (3 H, t, *J* 6.7 Hz, CH_3); *m/z* 284 (M^+, 1%), 266 (4), 253 (2), 173 (51), and 135 (100); (Found: M^+, 284.2361. $C_{17}H_{32}O_3$ requires *M*, 284.2351).

1,6-*Dimethoxy*-5-*oxatricyclo*[4.3.1.$0^{3,7}$]*decan*-9-*one* (**27**) *and* 1,6-*Dimethoxy*-5-*oxatricyclo*[4.3.1.$0^{3,7}$]*decan*-9-*ol* (**28**).—The chloronitriles (**24**) (94.6 mg, 0.368 mmol), sodium sulphide nonahydrate (100 mg) and potassium hydroxide (41.5 mg) were dissolved in 95% ethanol (2 ml), and the solution was heated under reflux for 48 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (5 ml) and ethyl acetate (5 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 5 ml), then acidified with 2M HCl and extracted with ethyl acetate (2 × 5 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, (5 ml), and brine (5 ml), dried (Na_2SO_4), and evaporated to give an oil. This was purified by preparative TLC with ethyl acetate–hexane (1:1) as eluant to give the ketone (**27**) as a solid, m.p. 91–93 °C (19.7 mg, 25%), and the mixture of alcohols (**28**) as an oil (18.2 mg, 23%).

The *ketone* (**27**); $\nu_{max}(CHCl_3)$ 1 760s cm^{-1}; $\delta_H(CDCl_3)$ 4.02–4.07 (1 H, dd, *J* 8.0, 3.4 Hz, H_9), 3.71–3.75 (1 H, d, *J* 8.0 Hz, $H_{9'}$) 3.24–3.25 (1 H, d, *J* 3.9 Hz, H_4), 3.43 (3 H, s, OCH_3), 3.41 (3 H, s, OCH_3), 2.83–2.90 (3 H, m, H_7, H_8), 2.46–2.50 (1 H, d, *J* 12 Hz, H_3), 2.30–2.35 (1 H, dd, *J* 12, 1 Hz, $H_{3'}$), 2.40–2.51 (1 H, dd, *J* 14.2, 1 Hz, H_6), and 2.30–2.36 (1 H, d, *J* 14.2 Hz, $H_{6'}$).

The *alcohols* (**28**); $\nu_{max}(CHCl_3)$ 3 600s and 2 930s cm^{-1}; $\delta_H(CDCl_3)$ 3.92–3.88 (1 H, dd, *J* 7.5, 3.3 Hz, H_9), 3.67–3.74 (1 H, ddd, *J* 7.5, 4.4, 2.1 Hz, $H_{9'}$), 3.31, (3 H, s, OCH_3), 3.18 (3 H, s, OCH_3), 3.24–3.34 (1 H, m, H_2), 2.0–2.5 (1 H, m, OH), and 1.5–2.4 (8 H, m); *m/z* 214 (M^+, 35%), 183 (50), 170 (68), and 99 (100); (Found: M^+, 214.1216. $C_{11}H_{18}O_4$ requires *M*, 214.1205).

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