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SYNTHESIS OF 4,4-DISUBSTITUTED CYCLOHEXENONES PART 1. BAEYER-VILLIGER FRAGMENTATION OF 1-METHOXYBICYCLO[2.2.2]OCT-5-ENONES

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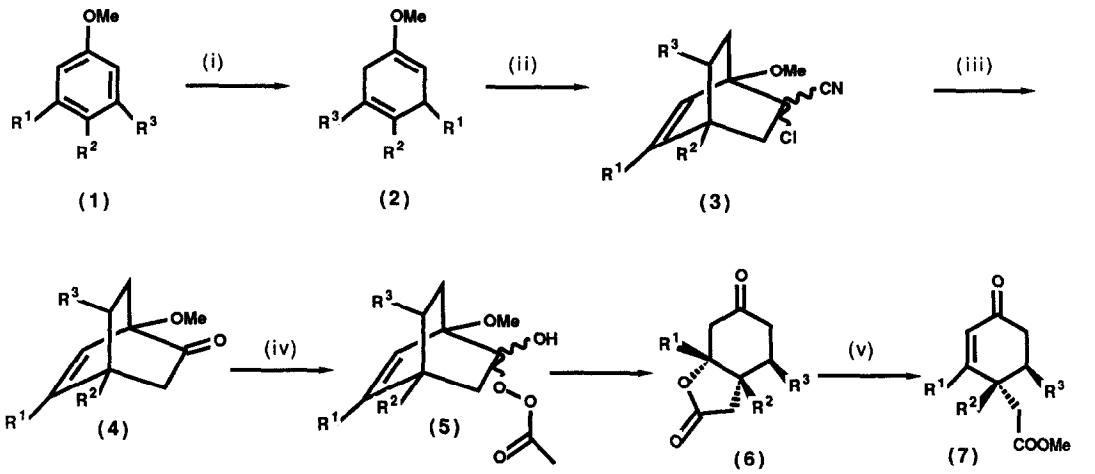
Summary: The sodium acetate-buffered peracetic acid oxidation of various 1-methoxybicyclo[2.2.2]oct-5-enones (**4a-f**), and (**14**), prepared by hydrolysis of the adducts (**3**) [(**13**)] derived from dihydroanisole derivatives (**2**) [(**12**)] and 2-chloroacrylonitrile leads to 4-substituted cyclohex-2-en-1-one 4-acetic acid derivatives (**7**) [(**15**)].

4,4-Disubstituted cyclohexenones have played an important part in the synthesis of many natural products. In particular most of the routes to the *Sceletium* alkaloids such as mesembrine and related compounds have relied on 4-aryl-4-aminoethylcyclohexenone intermediates.[1] Cyclohexenones have also featured in syntheses of trichodermin,[2] 9-pupukeanone,[3] and trichodermol.[4]

Many fundamentally different methods of construction of 4-substituted cyclohexenones have been reported. These include the early methods due to Stork, involving conjugate addition of an enamine to unsaturated ketones followed by intramolecular aldol cyclisation,[5] and the related asymmetric version due to Yamada,[6] and Martin's approach using a different method of forming enamines.[7] Martin has also closed the ring by intramolecular Wittig cyclisation.[8] Another popular method is the opening of β,γ-cyclopropylcyclohexanones.[9] Becker has exploited ozonolytic cleavage of acetals derived from deconjugated bicyclic enones.[10] Adducts derived from the Danishefsky diene[11] and related compounds[12] serve as useful precursors to cyclohexenones. The Stork-Danheiser[13] alkylation of enolates derived from 3-alkoxycyclohexenones has been applied by Kende[14] in an approach to the taxane diterpenes. γ-Alkylation of cyclohexenones, either through 1-alkoxycyclohexadienes[15] or involving the derived dienylium tricarbonyliron complexes[16] is a quite different strategy for preparing these versatile synthetic building blocks. Other contributions of note have emerged recently from the groups of Dauben,[17] Majetich,[18] and Meyers.[19]

The approach to cyclohexenones to be described in this paper is based on the fragmentation of bicyclo[2.2.2]octane derivatives which was pioneered by Birch over twenty years ago,[20] and which has been utilised by various workers in subsequent studies.[21] The general strategy[22] is illustrated in Scheme 1. Birch reduction of an appropriately substituted anisole (**1**) leads to the corresponding dihydro-derivative (**2**) which can be isomerised by a variety of acid-,[23] or base-catalysed,[24] or thermal[2,25,26] methods to the conjugated diene by a pathway involving shift of the enol ether double bond. We chose to follow the procedure developed by Evans[25] and subsequently exploited by Raphael[2] in which isomerisation of the diene occurs *in situ* in the presence of α-chloroacrylonitrile in refluxing benzene. Phenothiazine is used as a radical inhibitor and the dienophile undergoes cycloaddition to the conjugated diene as it is generated. There is generally no great

endo/exo diastereoselection in such reactions. Under forcing conditions the *exo*-chloro adduct (**3**; ***exo*-Cl**) can rearrange to the bicyclo[3.2.1]octanone (**8**).[2,27] Such rearrangements have been exploited by others in synthesis[28] and studied mechanistically.[29] Evans[25] developed an aqueous sodium sulphide procedure for the solvolysis of the chloronitrile adducts into the corresponding ketones. This has largely been followed by other workers in the field.[2,29,30] Other procedures involving aqueous potassium hydroxide solution[31] and potassium hydroxide in dimethylsulphoxide[32] have also been reported, but these are far less effective. All such hydrolyses apparently involve participation of the neighbouring π-bond,[27, 31] and the particular balance between required ketone and tricyclic by-product seems to be determined by the relative nucleophilicity of the solvolysis medium.



(a) $R^1 = R^3 = H$, $R^2 = Me$
(b) $R^1 = Me$, $R^2 = R^3 = H$
(c) $R^1 = R^2 = Me$, $R^3 = H$
(d) $R^1 = R^2 = R^3 = Me$
(e) $R^1 = R^2 = R^3 = H$
(f) $R^1, R^2 = -(CH_2)_5-$, $R^3 = H$

Reagents: (i) Birch reduction; (ii) 2-Chloroacrylonitrile, benzene, reflux; (iii) Sodium sulphide, potassium hydroxide, ethanol, reflux; (iv) Peracetic acid, acetic acid, sodium acetate; (v) Dimethyl sulphate, aqueous sodium hydroxide.

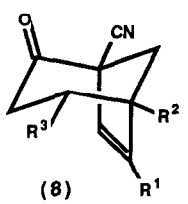
SCHEME 1

The final stage of the synthetic sequence (Scheme 1) involves Baeyer-Villiger fragmentation of the bicyclic enone to the rearranged fused lactone (**6**) and ultimately the cyclohexenone (**7**). The Baeyer Villiger oxidation of bicyclic ketones has been reviewed by Krow.[33] Meinwald[34] was the first person to recognise the fragmentation mode in the Baeyer-Villiger oxidation of bicyclo[2.2.2]octenones, and subsequent observation of this pathway has been recorded for a variety of electronically similar substrates.[35] This is to be contrasted with the behaviour of bicyclo[2.2.1]heptenone substrates whose oxidation forms the basis of Corey's seminal

route to prostaglandins.[36] For these compounds the intermediate lactone is usually isolable, and Lewis acids are required to promote the allylic rearrangement to the fused bicyclic lactone product. Such processes form the basis of several stereocontrolled routes to natural products as has been elegantly demonstrated by Grieco[37] and others.[38]

The general strategy was first tested with the ketone (**4a**) which was prepared from (**1a**), (**2a**), and (**3a**) according to the method reported by Evans.[25] Baeyer-Villiger oxidation of (**4a**) was carried out with two mol. equivalents of 40% peracetic acid in sodium acetate-buffered acetic acid over two days. Work-up of the reaction mixture yielded the rearranged lactone (**6a**) in 56% yield which could be converted into the cyclohexenone ester (**7a**)[9] in 91% yield by treatment with dimethyl sulphate in the presence of potassium carbonate. Direct work-up of the Baeyer-Villiger oxidation in this way afforded (**7a**) in a very respectable 80% from (**4a**). The use of other oxidants such as *m*-chloroperbenzoic acid or trifluoroperacetic acid for the Baeyer-Villiger oxidation was quite unsuccessful, resulting simply in epoxidation of the double bond in (**4a**). The optimum conditions were to add one mol. equivalent of peracetic acid to a solution of the ketone in buffered acetic acid, then to heat the reaction mixture at 50 °C for four hours. After the reaction mixture had cooled to room temperature another equivalent of per-acid was added, and the reaction was left for two days. The success of this general sequence with (**4a**) encouraged us to attempt the process with substituted methyl derivatives of (**4**; $R^1 = R^3 = H$; $R^2 = CH_2OH$, CH_2OAc, CH_2CH_2OH, CH_2CH_2OAc) but these all failed to undergo cycloaddition, presumably because of the increased steric demands of the modified substituent. This can to some extent be overcome by forcing the substituent into the ring plane as illustrated for the fused derivative (**3f**) which is smoothly formed in a cycloaddition reaction, and which can be converted into the ketone (**4f**) in the usual way. A related example of the use of this device is described below.

We have applied the general sequence to the bicyclo-octenones (**4a**), (**4b**), (**4c**), (**4d**), (**4e**), and (**4f**) to obtain the corresponding cyclohexenones (**7**) in yields ranging from 52-91 %. The results presented deserve some further comment. Some general difficulty was experienced in hydrolysis of the chloro-nitrile functionality to ketone. For example the procedure described[30] for (**4b**) was unreliable, and we managed to obtain reproducible, but nevertheless moderate yields, by carrying out the sodium sulphide solvolysis in 95% ethanol in the presence of two mol. equivalents of potassium hydroxide. Cycloaddition of various dienophiles to the trimethyl-substituted diene (**2d**) had previously been reported by Dastur[21a] and Masamune.[39] Only *anti*-approach of the dienophile to the CH_3 on the saturated bridge was observed by Dastur, whereas Masamune obtained mainly the *anti*-, but also some *syn*-product. In the present work predominantly the product of *anti*-addition of α-chloroacrylonitrile to (**3d**) was obtained. This led to a 8:1 ratio of the ketone solvolysis products (**9**) and (**10**) whose stereochemical assignment was made largely on the basis of n.O.e.



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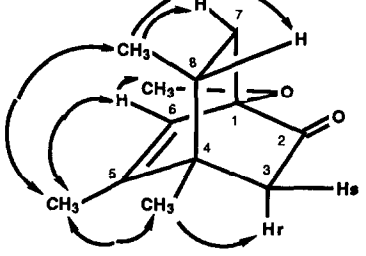

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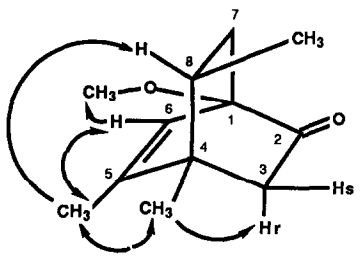
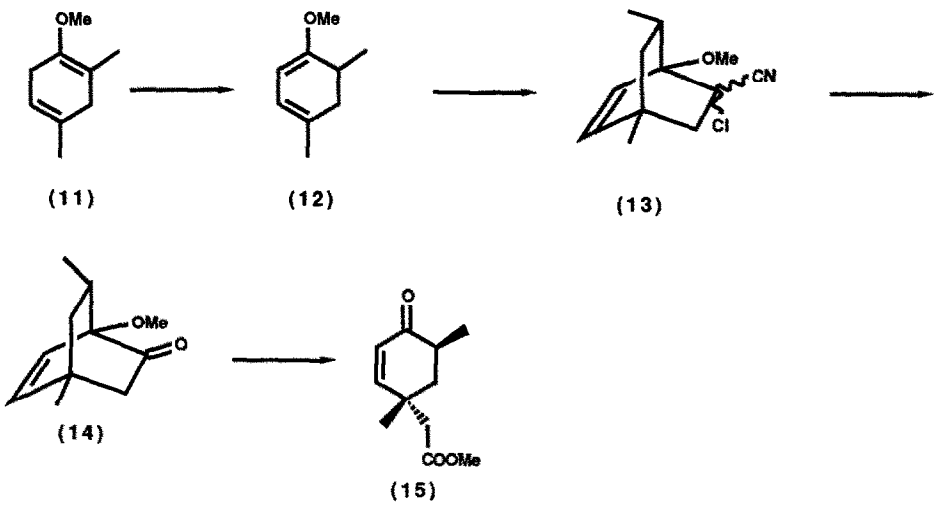


(10)

proton N.M.R. measurements as shown on the relevant structures. The chemical shift of the Me group in (**9**) which is *syn* to the double bond is characteristically at δ 0.8 whereas the corresponding group in (**10**) is at δ 1.0, a feature already noted by Masamune.[21d,e] Although the fused lactone (**6d**) was obtained from (**9**) in only modest yield, the direct work-up procedure for the Baeyer-Villiger oxidation afforded the relatively highly substituted cyclohexenone (**7d**) in respectable yield.

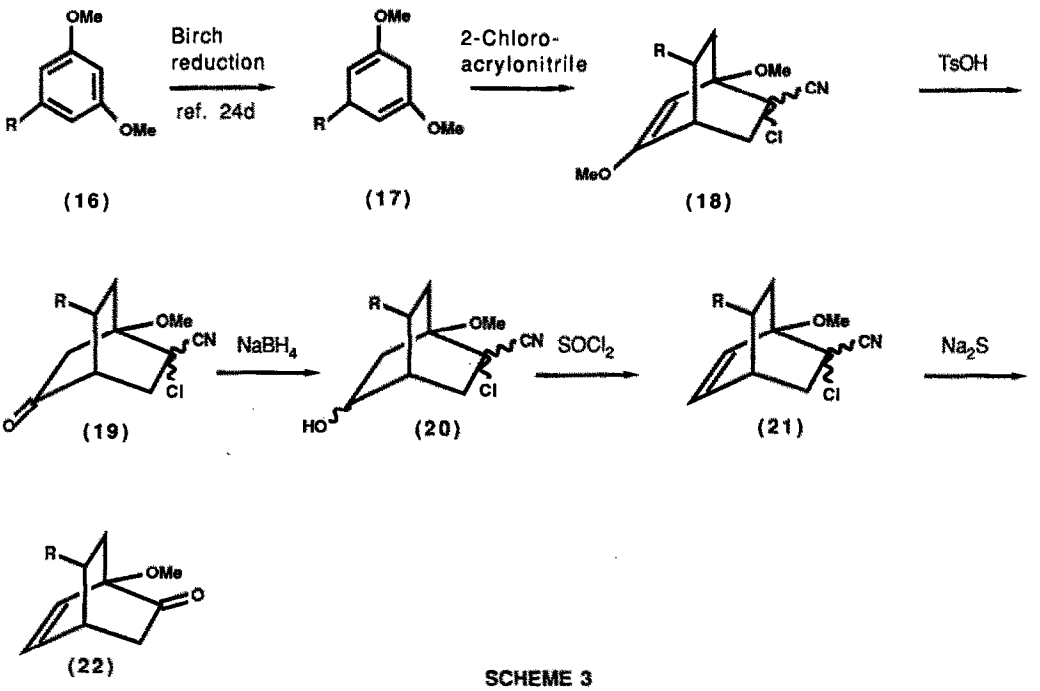
Under certain circumstances it is possible to introduce substituents at other positions in the bicyclo-octenone and hence into the target cyclohexenones. Thus the Birch reduction product (**11**)[3] of 2,4-dimethylanisole isomerises around the enol ether double bond to give (**12**) (Scheme 2). This undergoes essentially *anti*-selective cycloaddition to give the adduct (**13**) containing a 7-methyl substituent whose stereochemistry is established in the ketone (**14**) (δ 0.85 in the proton N.M.R. for the Me syn to the double bond). Baeyer-Villiger oxidation of (**14**) and work-up in the usual way gave the cyclohexenone (**15**).



(11) (12) (13) (14) (15)

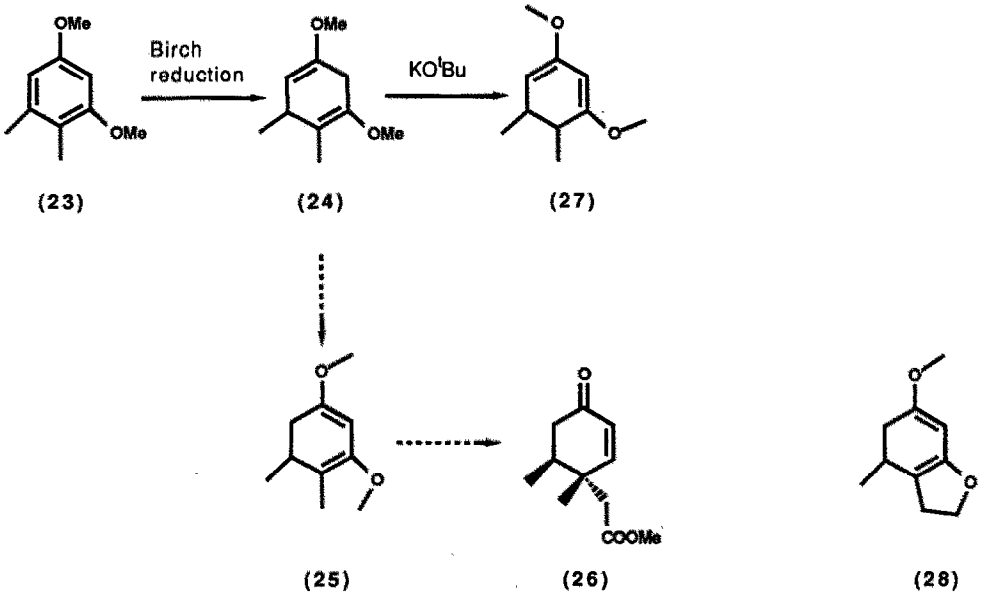
SCHEME 2

It is not possible to employ such a strategy to introduce a substituent at C-8 in (**4**) unless a symmetrical precursor such as (**2d**) is used. Thus isomerisation of a hypothetical Birch reduction product (**2**; $R^1 = R^2 =$ H; R^3 = alkyl) would inevitably lead to the more substituted diene and hence the adduct (**3**; R^1 = alkyl; $R^2 = R^3$ = H). However this problem can be overcome by using a removable substituent in the diene precursor. The general principle is illustrated in Scheme 3 in which the OMe group is employed as a removable group which directs the regioselectivity of the Birch reduction and the subsequent isomerisation. This strategy has been tested for the simplest example, resorcinol dimethyl ether (**16**; R = H). Birch reduction gave the required dihydro-product (**17**; R = H)[24c] which isomerised and underwent cycloaddition of the α-chloroacrylonitrile to give the adduct (**18**; R = H) which was not purified but was hydrolysed directly in acid to the ketone (**19**; R = H) in 72% yield. Removal of the carbonyl group was achieved by borohydride reduction to the mixture of alcohols (**20**; R = H), followed by thionyl chloride elimination to give (**21**; R = H) which is in fact identical to (**3e**) which has been converted into (**8e**).



SCHEME 3

Having established the general concepts for this sequence, we attempted to prepare the conjugated diene (25) by Birch reduction of (23) and isomerisation of (24). The cycloaddition sequence analogous to that shown in Scheme 3 when applied to (25) was expected to yield the cyclohexenone (26) which is an important precursor in the synthesis of the antifeedant ajugarin.[40] Unfortunately, potassium ^{t}butoxide-induced isomerisation of (24) gave exclusively the conjugated diene (27) which may indicate that the strain arising



from the known conformational preference[41] of the enol ethers in (**25**) is too high. The enol ether (**27**) enjoys apparently significantly less enol ether conformational strain than (**25**) (where the OMe group and the C-Me group are forced into the same region of space as a result of the preferred conformation of the enol ether) even though the double bond is di- as opposed to trisubstituted. A solution to this problem is to link these two carbons as shown in compound (**28**) and this has been achieved by both Masamune[42] and us.[27]

EXPERIMENTAL

M.p s were determined on a Köfler hot stage apparatus. Proton N.M.R. spectra were recorded at 250 MHz with a Bruker WM 250 or at 100 MHz with a Varian HA-100 or at 90 MHz with a Varian EM-390 spectrometer. I.R. spectra were recorded as a 2.5% w/v solution on a Perkin-Elmer 297 spectrometer. Mass spectra were recorded with A.E.I. MS 902 or 30 instruments. Microanalyses were performed by Mr D. Flory and staff at the University Chemical Laboratory, Cambridge. Thin layer chromatography was carried out on Merck kieselgel 60 GF254 plates coated to a thickness of 0.25 mm. Flash column chromatography was carried out on Merck kieselgel 60 (230-400 mesh).

6-Methyl-9-oxabicyclo[4.3.0]nonane-3,8-dione (6a).

1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one[25] (**4a**) (1.03 g, 0.062 mole) was dissolved in glacial acetic acid (5 ml) and anhydrous sodium acetate (0.5 g) was added. 40% Peracetic acid (3.4 ml, 0.124 mole) was added and the flask was stoppered and left at room temperature for 3 days. A further aliquot of 40% peracetic acid (1.2 ml, 0.062 mole) was added and the reaction mixture stood for a further 2 days. Then chloroform (40 ml) was added to the reaction mixture and the solution was washed with aqueous sodium sulphite, aqueous sodium hydrogen carbonate, and brine. The solution was dried over sodium sulphate and the solvent removed under reduced pressure to yield an oil. Recrystallisation from ethyl acetate/hexane gave a white solid (0.57 g, 56%) m.p. 74 - 75 °C; δ ($CDCl_3$) 4.6 (1H, t, J = 4Hz, H-1), 2.8 (2H, m, H-4), 2.6 (2H, q, J_{AB} = 14Hz, H-7), 2.4 (2H, m, H-2), 1.9 (2H, m, H-5), 1.4 (3H, s, Me-6); $\nu_{max.}$ ($CHCl_3$) 1780 and 1725 cm^{-1}; *m/z* 168 (M^+, 100%) and 96 (64). (Found: C, 64.1; H, 7.25. $C_9H_{12}O_3$ requires C, 64.3; H, 7.1%).

4-Methyl-1-oxocyclohex-2-en-4-acetic acid methyl ester (7a).[9]

6-Methyl-9-oxabicyclo[4.3.0]nonane-3,8-dione (**6a**) (0.5 g, 0.03 mole) was dissolved in acetone (20 ml). Anhydrous potassium carbonate (1 g) was added and the mixture heated at reflux for 1 hour. Dimethyl sulphate (4 ml, 0.042 mole) was then added and the mixture refluxed for 5 hours. The reaction mixture was cooled to room temperature and water (40 ml) added. The aqueous solution was extracted with chloroform (3 x 40 ml). The organic extracts were washed with brine (2 x 20 ml), dried over sodium sulphate, and the solvent removed *in vacuo* to give an oil. The oil was distilled to give the product (0.50 g, 91%), b.p. 50 °C/12 mm Hg (Kugelrohr) ; δ($CDCl_3$) 6.2 (1H, d, J = 9 Hz, H-2), 6.0 (1H, d, J = 9 Hz, H-3), 3.4 (3H, s, OMe), 2.1-1.3 (6H, m, H-5, 6, 7), 1.2 (3H, s, Me-4); $\nu_{max.}$ ($CHCl_3$) 1730, 1680, and 1620 cm^{-1}.

4-Methyl-1-oxocyclohex-2-en-4-acetic acid methyl ester (7a).[9]

1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one[25] (**4a**) (20 mg, 0.12 mmole) was dissolved in glacial acetic acid (1 ml). Sodium acetate anhydrous (0.1 g) and 40% peracetic acid (0.05 ml, 0.25 mmole) were added and the mixture heated at 50 °C for 3 hours. The mixture was cooled to room temperature and a

further aliquot of 40% peracetic acid (0.05 ml, 0.25 mmole) added. The reaction flask was stoppered and stood for 3 days at room temperature. Then acetone (10 ml), potassium carbonate (2 g), and dimethyl sulphate (2 ml) were added and the mixture heated at reflux for 1 hour. The solvent was removed under reduced pressure and water added to dissolve the salts. The aqueous solution was extracted with ether (3 x 10 ml). The ether was washed with brine, dried over sodium sulphate, and the solvent removed under reduced pressure to give an oil which was purified by preparative t.l.c. to give the ester (17 mg, 80%) identical with that previously prepared.

1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (4b).[30]

2-Chloro-1-methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-carbonitrile (**3b**), prepared according to the method of Monti,[74] (11.2 g, 0.053 mole) was dissolved in 95% ethanol (100 ml). Sodium sulphide nonahydrate (11.2 g, 0.047 mole) and potassium hydroxide (8 g, 0.143 mole) were added and the mixture heated at reflux for 16 hours. The reaction mixture was cooled to room temperature and ice-water (150 ml) was added and the aqueous solution extracted with ether (3 x 100 ml). The ether extracts were washed with brine (2 x 30 ml), dried over sodium sulphate, and the solvent removed *in vacuo* to give a brown oil. The oil was distilled under reduced pressure to give a colourless *oil* (4.0 g, 46%), b.p. 72-76 °C/0.3 mmHg (lit.,[30] 68-72 °C/0.2 mmHg); δ ($CDCl_3$) 5.7 (1H, br.s, H-6), 3.5 (3H, s, OMe), 2.7 (1H, br.s, H-4), 2.1 (2H, m, H-3), 1.9 (3H, d, J = 2 Hz, Me-5), 1.8-1.6 (4H, m, H-7, 8); $\nu_{max.}$ 1725 cm^{-1}.

3-Methyl-1-oxocyclohex-2-en-4-acetic acid methyl ester (7b).[43]

1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one[30] (**4b**) (0.5 g, 0.003 mole) was dissolved in glacial acetic acid (3 ml) and anhydrous sodium acetate (0.3 g) was added. 40% Peracetic acid (0.57 ml, 0.003 mole) was added with stirring. The mixture was warmed at 50 °C for 3 hours, allowed to cool to room temperature, and 40% peracetic acid (0.57 ml, 0.003 mole) added. The reaction was allowed to stand until complete by t.l.c. (4 days). Water (10 ml) was added to the reaction mixture and the solution was basified with 10% aqueous sodium hydroxide. Dimethyl sulphate (7.6 ml, 0.08 mole) was added and the solution stirred vigorously for 2 hours. The aqueous solution was extracted with ether (3 x 50 ml). The ether extracts were washed with brine and dried over sodium sulphate. The solvent was removed *in vacuo* to give an oil (0.5 g). The oil was distilled to give a colourless *liquid* (0.3 g, 59%) b.p. 125 °C/0.2 mmHg (Kugelrohr) (lit.,[43] 155 °C/0.6 mmHg); δ ($CDCl_3$) 5.9 (1H, s, H-2), 3.7 (3H, s, OMe), 3.4 (1H, s, H-4), 2.6-2.3 (6H, m, H-5, 6, 7), 2.0 (3H, d, J = 2 Hz, 3-Me); $\nu_{max.}$ ($CHCl_3$) 1720, 1630, and 1625 cm^{-1}.

2-Chloro-1-methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (3c).

2,5-Dihydro-3,4-dimethylanisole (**2c**) was prepared by Birch reduction of 3,4-dimethylanisole.[9] Compound (**2c**) (6.8 g, 0.05 mole) was dissolved in benzene (50 ml). 2-Chloroacrylonitrile (4.4 ml, 0.1 mole) and phenothiazine (50 mg) were added and the mixture heated at reflux for 16 hours under a nitrogen atmosphere. The mixture was cooled to room temperature and the solvent and high b.p. liquids were removed under reduced pressure to yield a light yellow crystalline *solid* (9.1 g, 81%). A sample was purified by preparative t.l.c. and recrystallised from ether/hexane m.p. 98-100 °C; δ ($CDCl_3$) 5.9 (1H, s, H-6), 3.5 (3H, s, OMe), 2.5-1.5 (6H, m, H-3, 7, 8), 1.9 (3H, d, J = 2 Hz, Me-5), 1.1 (3H, s, Me-4); $\nu_{max.}$ ($CHCl_3$) 2240 and 1645 cm^{-1}. *m/z* 162 (22%), 152 (45), and 137 (100). (Found: C, 63.5; H, 7.2; N, 6.09; Cl, 15.7. $C_{12}H_{16}ClNO$ requires C, 63.9; H, 7.1; N, 6.2; Cl, 16.7%).

1-Methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-one (4c).

2-Chloro-1-methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (**3c**) (16 g, 0.071 mole) was

dissolved in 95% ethanol (100 ml). Sodium sulphide nonahydrate (16 g, 0.067 mole) and potassium hydroxide (8 g, 0.143 mole) were added, and the mixture was heated at reflux for 16 hours. The mixture was cooled to room temperature and ice-water (150 ml) added. The aqueous mixture was extracted with ether (3 x 100 ml). The ether solution was washed with brine (2 x 30 ml) and dried over sodium sulphate. the solvent was removed under reduced pressure to give a brown oil which was distilled to give a *clear oil* (5.45 g, 43%), b.p. 78-80 °C/0.2 mmHg; δ ($CDCl_3$) 5.9 (1H, s, H-6), 3.5 (3H, s, OMe), 2.0 (2H, m, H-3), 1.9 (3H, d, J = 2 Hz, Me-5), 1.9-1.4 (4H, m, H-7, 8), 1.3 (3H, s, Me-4); $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; *m/z* 180 (M^+), 152, 138, and 124. (Found: C, 73.3; H, 9.00. $C_{11}H_{16}O_2$ required C, 73.3; H, 8.9%).

1-Methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-one (4c).

Small scale experiments to assess the effectiveness of various reagents in the hydrolysis reaction. 2-Chloro-1-methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (**3c**) (1.5 g, 0.007 mole) was dissolved in 95% ethanol (30 ml). Sodium sulphide nonahydrate (6 g, 0.026 mole) was added and the mixture heated at reflux for 17 hours. Water (30 ml) was added to dissolve salts and the aqueous solution extracted with ether (3 x 30 ml). The extracts were washed with brine (10 ml), dried over sodium sulphate and the ether removed under reduced pressure to give an oil (0.8 g). The oil was purified by column chromatography (silica/ether petrol ether) to yield an *oil* (0.47 g, 33%). 2-Chloro-1-methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (**3c**) (1.0 g, 0.0045 mole) was dissolved in 95% ethanol (20 ml). Sodium sulphide nonahydrate (1.0 g, 0.0043 mole) and potassium hydroxide (0.5 g, 0.009 mole) were added and the mixture was heated to reflux for 16 hours. Water (20 ml) was added to dissolve salts and the aqueous mixture extracted with ether (3 x 20 ml). The ether extracts were washed with brine (2 x 10 ml), dried over sodium sulphate, and the solvent removed under reduced pressure to give a brown oil (0.75 g). The oil was purified by column chromatography (silica: ether/petrol ether) to give a colourless *oil* (0.33 g, 41%).

3,4-Dimethyl-1-oxo-cyclohex-2-en-4-acetic acid methyl ester (7c).[9]

1-Methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-one (**4c**) (2 g, 0.011 mole) was dissolved in glacial acetic acid (10 ml) and anhydrous sodium acetate (1 g) was added. 40% Peracetic acid (2.1 ml, 0.011 mole) was added with stirring. The mixture was warmed at 50 °C for 3 hours, then allowed to cool to room temperature and a further aliquot of 40% peracetic acid (3.1 ml, 0.011 mole) added. The reaction was allowed to stand at room temperature until complete by t.l.c. (3 days). Water (20 ml) was added to the reaction mixture and then the aqueous solution was basified with 10% sodium hydroxide. Dimethyl sulphate (20 ml) was added and the solution stirred vigorously for 2 hours. The aqueous solution was extracted with ether (3 x 100 ml). The ether extracts were washed with brine (30 ml), and dried over sodium sulphate. The solvent was removed under reduced pressure to give an oil, which was distilled to give a clear *oil* (1.4 g, 60%), b.p. 100 °C/0.1 mm Hg (Kugelrohr) ; δ ($CDCl_3$) 5.8 (1H, s, H-2), 3.7 (3H, s, OMe), 2.6-1.4 (6H, m, H-3, 7, 8), 1.9 (3H, d, J = 2 Hz, Me-3), 1.25 (3H, s, Me-4); $\nu_{max.}$ ($CHCl_3$) 1730, 1660, and 1600 cm^{-1}.

2-Chloro-1-methoxy-4,5,8-trimethylbicyclo[2.2.2]-oct-5-en-2-carbonitrile (3d).

2,5-Dihydro-3,4,5-trimethylanisole (**2d**) (10 g, 0.066 mole) was prepared by Birch reduction of 3,4,5-trimethylanisole[21a] and was dissolved in benzene (100 ml). 2-Chloroacrylonitrile (12 ml, 0.27 mole) and phenothiazine (50 mg) were added and the mixture was heated at reflux for 16 hours under a nitrogen atmosphere. The reaction was cooled to room temperature and the solvent and high b.p. liquids were removed under reduced pressure to give a yellow crystalline *solid* (10.9 g, 67%). A sample was purified by

preparative t.l.c. and recrystallised from ether/hexane m.p. 72-74 °C; δ ($CDCl_3$) 5.9 (1H, s, H-6), 3.6 (3H, s, OMe), 2.5-2.1 (5H, m, H-3, 7, 8), 1.8 (3H, d, J = 2 Hz, Me-5), 1.2 (3H, s, Me-4), 0.8 (3H, d, J = 7 Hz, Me-7); $\nu_{max.}$ ($CHCl_3$) 2220 and 1650 cm^{-1}; *m/z* 203 (35%), 188 (64), 174 (40), and 137 (100). (Found: C, 65.1; H, 7.4; N, 5.7; Cl, 14.9%. $C_{13}H_{18}ClNO$ requires C, 65.1; H, 7.5; N, 5.9; Cl, 14.9%).

1-Methoxy-4,5, anti-8-trimethylbicyclo[2.2.2]oct-5-en-2-one (9) and 1-Methoxy-4,5, syn-8-trimethylbicyclo[2.2.2]oct-5-en-2-one (10).

2-Chloro-1-methoxy-4,5,8-trimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (**3d**) (2.5 g, 0.01 mole) as a 8:1 mixture of *anti*- and *syn*-isomers was dissolved in 95% ethanol (25 ml). Sodium sulphide nonahydrate (2.5 g, 0.01 mole) and potassium hydroxide (1.25 g, 0.02 mole) were added and the mixture heated at reflux for 16 hours. The reaction mixture was cooled to room temperature and ice/water (75 ml) was added. The aqueous mixture was extracted with ether (3 x 25 ml). The ether extracts were washed with brine (15 ml) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a brown oil which was distilled to give (**9**) as a colourless *oil* (1.1 g, 55%) b.p. 70 °C/0.1 mmHg (Kugelrohr); δ ($CDCl_3$, 400 MHz) 5.9 (1H, s, H-6), 3.5 (3H, s, OMe), 2.05 & 1.95 (2H, AB q, J = 18 Hz, H-3) 1.9-1.8 (2H, m, H-7), 1.8 (3H, d, J = 2 Hz, Me-5), 1.25 (1H, m, H-8), 1.2 (3H, s, Me-4), 0.8 (3H, d, J = 7 Hz, Me-8); $\nu_{max.}$ ($CHCl_3$) 1735 and 1600 cm^{-1}; *m/z* 194 (M^+), 166, and 152. (Found: C, 74.2; H, 9.2. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%). N.M.R. data ($CDCl_3$, 400 MHz) for (**10**): δ 5.85 (1H, br. s, H-6), 3.5 (3H, s, OMe), 2.25 & 2.15 (2H, AB q, J = 18 Hz, H-3), 1.9-1.8 (2H, m, H-7), 1.8 (3H, d, J = 2 Hz, Me-5), 1.3 (1H, m, H-8), 1.1 (3H, s, Me-4), 1.0 (3H, d, J = 7 Hz, Me-8).

1,5,6-Trimethyl-9-oxabicyclo[4.3.0]nonan-3,8-dione (6d).

1-Methoxy-4,5,8-trimethylbicyclo[2.2.2]oct-5-en-2-one (**9**) (0.11 g, 56 mmole) was dissolved in glacial acetic acid (1 ml) and anhydrous sodium acetate (0.1 g) added. 40% Peracetic acid (0.11 ml, 57 mmole) was added and the mixture heated at 50 °C for 4 hours. The reaction mixture was then allowed to cool to room temperature and a further aliquot of 40% peracetic acid (0.11 ml, 57 mmole) added. The mixture was allowed to stand at room temperature until reaction was complete by t.l.c. (4 days). Chloroform (20 ml) was added to the reaction mixture. The solution was washed with aqueous sodium hydrogen carbonate, brine (10 ml), and dried over sodium sulphate. The solvent was removed under reduced pressure to give an oil which crystallised from chloroform/hexane to give a white *solid* (19 mg, 17%) m.p. 104-105 °C; δ ($CDCl_3$) 3.0-2.2 (7H, H-2, 4, 5, 7), 1.4 (3H, s, Me-1), 1.2 (3H, s, Me-6), 1.0, 3H, d, J = 7 Hz, Me-5); $\nu_{max.}$ ($CHCl_3$) 1770 and 1730 cm^{-1}; *m/z* 196 (M^+), 180 and 167. (Found: C, 67.1; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.4; H, 8.2%).

3,4,5-Trimethyl-1-oxocyclohex-2-en-4-acetic acid methyl ester (7d).

1-Methoxy-4,5,8-trimethylbicyclo[2.2.2]oct-5-en-2-one (**9**) (41 mg, 0.21 mmole) was dissolved in glacial acetic acid (1 ml). Sodium acetate (0.1 g) and 40% peracetic acid (0.05 ml, 0.25 mmole) were added. The mixture was heated at 50 °C for 2 hours. Then a further aliquot of 40% peracetic acid (0.5 ml, 0.25 mmole) was added and the solution stood at room temperature for 2 days. Then acetone (10 ml), potassium carbonate (2 g) and dimethyl sulphate (2 ml) were added and the mixture heated at reflux for 2 hours. The solvent was removed under reduced pressure and water added to dissolve the salts. The aqueous solution was extracted with ether. The ether extracts were washed with brine, dried over sodium sulphate, and the solvent removed to given an oil which was purified by preparative t.l.c. to give the ester (23 mg, 52%), b.p. 110 °C/0.1 mm Hg; δ ($CDCl_3$) 5.9 (1H, s, H-2), 3.7 (3H, s, OMe), 2.6 (2H, m, H-7), 2.5-2.3 (3H, m, H-5, 6), 2.0 (3H, d, J = 2 Hz, Me-3), 1.1 (3H, s, Me-4), 1.0 (3H, d, J = 7 Hz, Me-5); $\nu_{max.}$ ($CHCl_3$)

1735, 1665 and 1625 cm^{-1}; *m/z* 210 (M^+), 195, and 179. (Found: C, 68.8; H, 8.8. $C_{12}H_{18}O_3$ requires C, 68.6; H, 8.6%).

1-Oxocyclohex-2-en-4-acetic acid methyl ester (7e).[44]

1-Methoxybicyclo[2.2.2]oct-5-en-2-one (**4e**)[25] (82mg, 0.54mmole) was dissolved in glacial acetic acid (2ml). 40% Peracetic acid (0.11ml, 0.55mmole) and anhydrous sodium acetate (0.2g) were added and the mixture heated at 50°C for 3 hours. Then the reaction was cooled to room temperature and a further aliquot (0.11ml, 0.55 mmole) of peracetic acid added. The reaction was allowed to stand at room temperature for 3 days. Then acetone (15ml), anhydrous potassium carbonate (5 g), and dimethyl sulphate (3 ml) were added. The mixture was heated at reflux for 3 hours. The solvent was removed under reduced pressure and water added to dissolve salts. The aqueous solution was extracted with ether. The extracts were washed with brine, dried over sodium sulphate, and solvent removed under reduced pressure to give an oil which was purified by preparative t.l.c. (SiO_2/ether) to give the *ester* (77mg, 85%); δ ($CDCl_3$) 6.8 (1H, m, H-2), 6.0 (1H, m, H-3), 3.7 (3H, s, OMe), 2.5-1.7 (7H, m, H-4,5,6,7); $\nu_{max.}$ ($CHCl_3$) 1730 and 1675 cm^{-1}.

1-Methoxytricyclo[3.2.2.1]undec-5-en-2-one (4f).

2-Chloro-1-methoxytricyclo[3.2.2.1]undec-5-en-2-carbonitrile (**3f**)[28a] (23.7g, 0.1mole) was dissolved in 95% ethanol (200ml). Sodium sulphide nonahydrate (25g, 0.104mole) and potassium hydroxide (12g, 0.21mole) were added and the mixture heated at reflux for 17 hours. Most of the solvent was removed under reduced pressure and water (100ml) was added. The aqueous mixture was extracted with ether (3 x 50ml). The ether extracts were washed with brine (20ml) and dried over sodium sulphate. The solvent was removed under reduced pressure and the product distilled to yield a clear *oil* (9.8g, 54%) b.p. 130-4 °C/0.3 mm Hg; δ ($CDCl_3$) 5.9 (1H, br.s, H-6), 3.5 (3H, s, OMe), 2.5-1.4 (12H, m, H-3,7,8,9,10,11); $\nu_{max.}$ ($CHCl_3$) 1720cm^{-1}; *m/z* 192 (M^+), 164 and 150; (Found: C, 75.0; H, 8.8. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

Baeyer-Villiger Oxidation of the Ketone (4f).

The ketone (**4f**) (300 mg, 1.56 mmole) was dissolved in glacial acetic acid (3 ml) containing sodium acetate (300 mg) and 40% peracetic acid (0.8 ml, 4.16 mmole) and the reaction mixture was heated at 50 °C for 4 hours. The reaction mixture was allowed to cool to room temperature, and a further quantity of 40% peracetic acid (0.8 ml, 4.16 mmole) was added. After a further reaction time of 2 days at room temperature acetone (10 ml) was added, followed by potassium carbonate (2.5 g) and dimethyl sulphate (6 ml). The mixture was heated to reflux for 2 hours, then it was cooled to room temperature, and the solvent was removed. Water was added to the residue and the aqueous layer was extracted with ether. The combined ether extracts were dried over sodium sulphate and the ether was removed on the rotary evaporator to yield the *indenone ester (7f)* as a colourless oil (148 mg, 65%); δ ($CDCl_3$) 5.8 (1H, br. s.), 3.6 (3H, s), 2.8 (2H, m), 2.5 - 1.1 (10H, m); $\nu_{max.}$ 1730, 1675 and 1620 cm^{-1}.

2-Chloro-1-methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-en-2-carbonitrile (13).

3,6-Dihydro-2,4-dimethylanisole (**11**) (14 g, 0.1 mole), prepared by Birch reduction of 2,4-dimethylanisole[3] was dissolved in benzene (150 ml). 2-Chloroacrylonitrile (18 ml, 0.2 mole) and phenothiazine (100 mg) were added and the mixture heated at reflux for 17 hours. The solvent and high b.p. liquids were removed under reduced pressure to give an *oil* (15.5 g, 69%); δ ($CDCl_3$) 6.1 (2H, s, H-5, 6), 3.7 (3H, s, OMe), 2.6-1.7 (5H, m, H-3, 7, 8), 1.1 (3H, s, Me-4), 0.9 (3H, d, J = 7 Hz, Me-7). This material was difficult to purify and was carried through to the *ketone* (**14**).

1-Methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-en-one (14).

2-Chloro-1-methoxy-4,7-dimethylbiyclo[2.2.2]oct-5-en-2-carbonitrile (**13**) (9 g, 0.04 mole) was dissolved in 95% ethanol (60 ml). Sodium sulphide nonahydrate (13.5 g, 0.056mole) and potassium hydroxide (4.5 g, 0.08mole) were added and the mixture heated at reflux for 17 hours. The solvent was removed under reduced pressure and water (100 ml) added to dissolve the salts. The aqueous solution was extracted with ether (3 x 50 ml). The ether solution was washed with brine (50 ml) and dried over sodium sulphate. The solvent was removed under reduced pressure to give an oil which was distilled to yield the *ketone* (4.5 g, 69%), b.p. 72-76 °C/0.05 mm Hg; δ ($CDCl_3$) 6.1 (2H, m, H-5, 6), 3.5 (3H, s, OMe), 2.3-1.7 (5H, m, H-3, 7, 8), 1.2 (3H, s, Me-4), 0.85 (3H, d, J = 7 Hz, Me-7); $\nu_{max.}$ ($CHCl_3$) 1725 and 1610 cm^{-1}; *m/z* 180 (M^+), 138 and 123. (Found: C, 73.5; H, 8.68. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.9%).

4,6-Dimethyl-1-oxocyclohex-2-en-4-acetic acid methyl ester (15).[3]

1-Methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-en-2-one (**14**) (217mg, 1.2 mmole) was dissolved in glacial acetic acid (2ml). 40% Peracetic acid (0.25ml, 1.3mmole and anhydrous sodium acetate (0.2 g) were added and the mixture heated at 50 °C for 3.5 hours. The reaction was cooled to room temperature and a further aliquot of peracetic acid (0.25 ml) added. The mixture was allowed to stand at room temperature for 3 days. Then acetone (20 ml) and potassium carbonate (5 g) were added. Dimethyl sulphate (3 ml) was also added and the mixture heated at reflux for 2 hours. The solvent was removed under reduced pressure and water added to dissolve salts. The aqueous solution was extracted with ether. The extracts were washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure to give an oil which was distilled to give the *ester* (143 mg, 60%), b.p. 110 °C/0.15 mm Hg (Kugelrohr); δ ($CDCl_3$) 6.2 (1H, d, J = 10 Hz, H-2), 6.0 (1H, d, J = 10 Hz, H-3) 3.6 (3H, s, OMe), 3.5 (3H, s, OMe), 2.5-1.7 (5H, m, H-5,6,7), 1.3 (3H, s, Me-4), 1.2 (3H, s Me), and 1.0 (3H, d, J = 7 Hz, Me-6); $\nu_{max.}$ ($CHCl_3$) 1730, 1660, and 1610 cm^{-1}.

2-Chloro-2-cyano-1-methoxybicyclo[2.2.2]octan-5-one (19; R = H).

2,5-Dihydro-1,4-dimethoxybenzene (**17; R = H**)[24d] (14.3 g, 0.1mole) was dissolved in benzene (60ml). 2-Chloroacrylonitrile (16 ml, 0.2 mole) and phenothiazine (100 mg) were added and the mixture heated at reflux for 16 hours under a nitrogen atmosphere. The solvent and high b.p. liquids were removed under reduced pressure to give an oil (25.5 g). Crude enol ether (13.4 g) was dissolved in ether (100 ml), washed with 3M hydrochloric acid (2 x 50 ml), 10% aqueous sodium hydroxide (3 x 50 ml), and dried over sodium sulphate. The solvent was removed under reduced pressure to give product (9.5 g). Recrystallisation from ether/hexane gave *crystals* (3.9 g, 35%), m.p. 101-103 °C. Crude enol ether (0.5 g) was dissolved in ether (5 ml) and *p*-toluene sulphonic acid (0.4 g) was added. The mixture was stirred at room temperature for 2 hours. The ether solution was washed with 10% sodium hydroxide and (2 x 5 ml), brine (5 ml), and dried over sodium sulphate. The solvent was removed under reduced pressure to give the *ketone* as white crystals (0.3 g, 72%), m.p. 102-4 °C; δ ($CDCl_3$) 3.4 (3H, s, OMe), 3.0 (1H, s, H-4), 2.8 (2H, m, H-6), 2.4 (2H, m, H-3), 2.3-2.0 (4H, m, H-7,8); $\nu_{max.}$ ($CHCl_3$) 1730 and 1600cm^{-1}; *m/z* 215 and 213 (M^+), 178, and 126. (Found: C, 56.5; H, 5.61; N, 6.38. $C_{10}H_{12}ClNO_2$ requires C, 56.2; H, 5.62; N, 6.56%).

2-Chloro-2-cyano-1-methoxybicyclo[2.2.2]octan-5-ol (20; R = H).

2-Chloro-2-cyano-1-methoxybicyclo[2.2.2]octan-5-one (**19; R = H**) (3.9 g, 0.018 mole) was dissolved in methanol (70 ml). A solution of sodium borohydride (0.7 g, 0.018 mole) in 10% aqueous

sodium hydroxide (10 ml) was added dropwise with stirring to the ice-cooled solution. The mixture was allowed to warm to room temperature and stand for 45 mins. The mixture was then acidified with 3M hydrochloric acid. The methanol was removed under reduced pressure. The aqueous solution was extracted with ether (3 x 50 ml). The ether extracts were washed with sodium hydrogen carbonate, brine, and dried over sodum sulphate. The ether was removed under reduced pressure to give the epimeric mixture of *alcohols* as a white solid (3.7g, 94%), m.p. 106-8 °C; δ ($CDCl_3$) 4.1 (1H, br.s, OH), 3.4 (3H, s, OMe), 3.0 (1H, br.s, H-4), 2.8-2.6 (5H, m, H-3,5,6), 2.2-1.9 (4H, m, H-7,8); $\nu_{max.}$ ($CHCl_3$) 3600 and 3500cm^{-1}; *m/z* 217 and 215 (M^+, 2 and 10%), 162 (4), and 100 (100). (Found: C, 55.9; H, 6.4; N, 6.3; M^+ *m/z* 217.0668. $C_{10}H_{14}ClNO_2$ requires C, 55.7; H, 6.5; N, 6.5%; M 217.0684).

2-Chloro-1-methoxybicyclo[2.2.2]oct-5-en-2-carbonitrile (4e).[25]

2-Chloro-2-cyano-1-methoxybicyclo[2.2.2]octan-5-ol (**20; R = H**) (357 mg, 1.66 mmole) was dissolved in thionyl chloride (8 ml) and the solution heated at reflux for 48 hours. The thionyl chloride was removed under reduced pressure. Ether (30 ml) was added to the residue and the ether solution washed with aqueous sodium hydrogen carbonate (2 x 10 ml), brine (10 ml), and dried over sodium sulphate. The ether was removed under reduced pressure to give an oil. The product was purified by preparative t.l.c. to give the bicyclic ketone (**4e**) (142 mg, 43%) identical by t.l.c. and spectral data to that prepared directly from anisole.[25]

1,5-Dimethoxy-2,3-dimethylbenzene (23).

1,5-Diacetoxy-2,3-dimethylbenzene[45] (28 g, 0.13 mole) was mixed with 10% aqueous sodium hydroxide (330 ml) and heated at reflux for 1.5 hours. The solution was cooled to room temperature and dimethyl sulphate (60 ml) was added dropwise. The mixture was stirred for 17 hours. Then concentrated aqueous ammonia (30 ml) was added and the mixture stirred for 0.5 hour. The aqueous solution was extracted with ether (3 x 150 ml). The extracts were washed with brine (30 ml), and dried over magnesium sulphate. The ether was removed under reduced pressure to give an *oil* (19 g, 88%); δ ($CDCl_3$) 6.3 (2H, s, H-4,6) 3.8 (6H, s, OMe), 2.2 (3H, s, Me-2), 2.0 (3H, s, Me-3). $\nu_{max.}$ ($CHCl_3$) 2815, 1610, and 1600 cm-1.

3,6-Dihydro-1,5-dimethoxy-2,3-dimethylbenzene (24).

1,5-Dimethoxy-2,3-dimethylbenzene (2.5 g, 0.015 mole) in ethanol (15 ml) was added to liquid ammonia (60 ml). Lithium (1 g, 0.14 mole) was added in small portions until a permanent blue colour appeared, and during the next 3 hours to maintain the colour. The mixture was allowed to reflux during this time. The colour was then allowed to discharge and the ammonia evaporate. Ice-water (400 ml) was added to dissolve the salts and the aqueous solution was extracted with ether (3 x 100 ml). The extracts were washed with brine (40 ml), dried over sodium sulphate, and the solvent removed under reduced pressure to yield an *oil* (1 g, 40%); δ ($CDCl_3$) 4.5 (1H, br.s, H-6), 3.5 (6H, s, OMe), 2.8 (3H, m, H-2,5), 1.7 (3H, s, Me-4) 1.1 (3H, d, J = 7 Hz, Me-5); $\nu_{max.}$ ($CHCl_3$) 1705 and 1670 cm^{-1}.

Base-catalysed isomerisation of 3,6-dihydro-1,5-dimethoxy-2,3-dimethylbenzene (24).

3,6-Dihydro-1,5-dimethoxy-2,3-dimethylbenzene (**24**) (20 mg, 0.15 mmole) was dissolved in dimethyl sulphoxide (2 ml). Potassium *tert.*-butoxide (25mg, 0.2 mmole) was added and the mixture stirred for 4 hours at room temperature. The solvent was removed under reduced pressure. The product was distilled off the salts (0.1mm Hg, 100 °C Kugelrohr). Proton N.M.R. showed the product to be *2,3-dihydro-1,5-dimethoxy-2,3-dimethylbenzene* (**27**). δ ($CDCl_3$) 5.3 (2H, m, H-4,6), 3.7 (6H, s, OMe), 1.6 (2H, m, H-2,3), 1.3 (3H, d, J = 7 Hz, Me-2), 1.1 (3H, d, J = 7 Hz, Me-3).

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REFERENCES

1. M. Shamma and H.R. Rodriguez, *Tetrahedron*, 1968, **24**, 6583; S. Yamada and G. Otani, *Chem. Pharm. Bull.*, 1973, **21**, 2130; S.F. Martin and G.W. Phillips, *J. Org. Chem.*, 1978, **43**, 3792; S.F. Martin, T.A. Puckette, and J.A. Colapret, *ibid*, 1979, **44**, 3391; H.F. Strauss and A. Wiechers, *Tetrahedron Lett.*, 1979, 4495; K. Psotta and A. Wiechers, *Tetrahedron*, 1979, **35**, 255; S. Danishefsky, J. Morris, G. Mullen, and R. Gannill, *J. Am. Chem. Soc.*, 1980, **102**, 2838.

2. E.W. Colvin, S. Malchenko, R.A. Raphael, and J.S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1989.

3. G.A. Schiehser and J.D. White, *J. Org. Chem.*, 1980, **45**, 1864.

4. W.C. Still and M.Y. Tsai, *J. Am. Chem. Soc.*, 1980, **102**, 3654.

5. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 1968, **85**, 207.

6. G. Otani and S. Yamada, *Chem Pharm. Bull.*, 1973, **21**, 2125.

7. S.F. Martin and R. Gompper, *J. Org. Chem.*, 1974, **39**, 2814; S.F. Martin, *ibid*, 1976, **41**, 3337; S.F. Martin, T.S. Chon, and C.W. Payne, *ibid*, 1977, **42**, 2520.

8. S.F. Martin and S.R. Desai, *J. Org. Chem.*, 1978, **43**, 4673.

9. R.D. Stipanovic and R.B. Turner, *J. Org. Chem.*, 1968, **33**, 3261.

10. D. Becker, J. Kalo, and N.C. Brodsky, *J. Org. Chem.*, 1978, **43**, 2562.

11. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807.

12. I. Fleming and A. Percival, *J. Chem. Soc., Chem. Commun.*, 1978, 178.

13. G. Stork and R.L. Danheiser, *J. Org. Chem.* 1973, **38**, 1775.

14. A.S. Kende, M. Benechie, D.P. Curran, and P. Fludzinski, *Tetrahedron Lett.*, 1979, 4513.

15. I. Paterson and L.G. Price, *Tetrahedron Lett.*, 1981, 2833.

16. A.J. Birch, K.B. Chamberlain, M.A. Haas, and D.J. Thompson, *J. Chem. Soc., Perkin Trans.* 1, 1973, 1882; A.J. Pearson, *Acc. Chem. Res.*, 1980, **13**, 463.

17. W.G. Dauben, G. Shapiro, and L. Luders, *Tetrahedron Lett.*,1985, **26**, 1429.

18. G. Majetich, K. Hull, J. Defamo, and R. Desmond, *Tetrahedron Lett.*, 1985, **26**, 2747.

19. A.I. Meyers and B.A. Lefker, *Tetrahedron*, 1987, **43**, 5663 and references cited therein.

20. A.J. Birch and J.S. Hill, *J. Chem. Soc. C*, 1966, 419; *ibid*, 1967, 125.

21. (a) K.P. Dastur, *J. Am. Chem. Soc.*, 1974, **96**, 2605; (b) M.R. Roberts and R.H. Schlessinger, *ibid*, 1981, **103**, 724; (c) B.C. Uff, M.J. Powell, and A.C.W. Curran, *J. Chem. Soc., Chem. Commun.*, 1980, 1059; (d) A. Murai, S. Sato, and T. Masamune, *Tetrahedron Lett.*, 1981, 1033; (e) A. Murai, S. Sato, and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1981, 904; (f) T. Ibuka, Y. Mori, and Y. Inubushi, *Chem. Pharm. Bull.*, 1978, **26**, 2442; (g) K. Pramod and G.S.R. Subba Rao, *Indian J. Chem.*, 1982, **21B**, 984.

22. Preliminary communication: A.B. Holmes and N.C. Madge, *J. Chem. Soc., Chem. Commun.*, 1980, 956.

23. A.J. Birch and K.P. Dastur, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1650.

24. (a) A.J. Birch, E.M.A. Stronkry, and F. Stansfield, *J. Chem. Soc.*, 1961, 5376; (b) A.J. Birch, J.M.H. Graves, and J.B. Siddall, *ibid*, 1963, 4234; (c) A.J. Birch and B. McKague, *Aust. J. Chem.*, 1970, **23**, 341;

(d) I. Alfaro, W. Ashton, L.D. McManus, R.C. Newstead, K.L. Rathbone, N.A.J. Rogers, and W. Kerrick, *Tetrahedron*, 1970, **26**, 201.

25. D.A. Evans, W. Scott, and L.K. Truesdale, *Tetrahedron Lett.*, 1972, 121.

26. M. Demuth, *Helv. Chim. Acta*, 1980, **63**, 2434.

27. R.S.J. Clark, A.B. Holmes, and V.G. Matassa, *manuscript submitted for publication.*

28. (a) Y. Yamada, H. Nagaoka, and M. Kimura, *Synthesis*, 1977, 581; (b) S.A. Monti and S.C. Chen, *J. Org. Chem.*, 1979, **44**, 1170.

29. D.H. Hua, W.-Y. Gung, R.A. Ostrander, and F. Takusagawa, *J. Org. Chem.*, 1987, **52**, 2509.

30. S.A. Monti, S.-C. Chen, Y.-L. Yang, S.-S. Yuan, and O.P. Bourgeois, *J. Org. Chem.*, 1978, **43**, 4062.

31. J. Paasivirta and H. Krieger, *Suomen Kemstileti*, **B**, 1965, **38**, 182.

32. P.K. Freeman, D.M. Ball, and D.J. Brown, *J. Org. Chem.*, 1968, **33**, 2211.

33. G.R. Krow, *Tetrahedron*, 1981, **37**, 2697.

34. J. Meinwald, M.C. Seidel, and B.C. Cadoff, *J. Am. Chem. Soc.*, 1958, **80**, 6303; J. Meinwald and E. Frauenglass, *ibid*, 1960, **82**, 5235.

35. B. Belleau and T.F. Gallagher, *J. Am. Chem. Soc.*, 1952, **74**, 2816; I.J. Borowitz, G.J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, 1968, **33**, 2013; S.A. Monti and C.K. Ward, *Tetrahedron Lett.*, 1971, 697; H. Miura, K.A. Hirao and O. Yonemitsu, *Tetrahedron*, 1978, **34**, 1805; E. Vedejs, D.A. Engler, and J.E. Teschow, *J. Org. Chem.*, 1978, **43**, 188; M.E. Jung and S.J. Miller, *J. Am. Chem. Soc.*, 1981, **103**, 1984.

36. E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *J. Am. Chem. Soc.*, 1971, **93**, 1491; E.J. Corey and G. Moinet, *ibid*, 1973, **95**, 1785.

37. P.A. Grieco, C.S. Pogonowski, S.D. Burke, M. Mishizawa, M. Miyashita, Y. Masaki, C.L.J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, 1977, **90**, 4111; P.A. Grieco, Y. Ohfune, and G. Majetich, *ibid*, 7393; P.A. Grieco, T. Takigawa, and D.R. Moore, *ibid*, 1979, **101**, 4380; P.A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *ibid*, 4749; P.A. Grieco, E. Williams, H. Tanaka, and S. Gilman, *J. Org. Chem.*, 1980, **45**, 3537; P.A. Grieco and Y. Ohfune, *ibid*, 2251; P.A. Grieco, T. Takigawa, and W.J. Schillinger, *ibid*, 2247.

38. B.M. Trost, P.R. Bernstein, and P.C. Funfschilling, *J. Am. Chem. Soc.*, 1979, **101**, 4378; A.E. Greene, C. Le Drian, and P. Crabbe, *ibid*, 1980, **102**, 7583; A. Barco, S. Benetti, G.P. Pollini, P.G. Baraldi, and C. Gandolfi, *J. Org. Chem.*, 1980, **45**, 4776.

39. A. Murai, S. Sato, and T. Masamune, *Chem. Lett.*, 1981, 429.

40. S.V. Ley, N.S. Simpkins, and A.J. Whittle, *J. Chem. Soc., Chem. Commun.*, 1981, 1001; *ibid*, 1983, 503.

41. A.J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen," Springer-Verlag, Berlin, 1983; K.L. Brown, L. Damm, J.D. Dunitz, A. Eschenmoser, R. Hobi, and C. Kratky, *Helv. Chim. Acta*, 1978, **61**, 3108; J.D. Mersh and J.K.M. Sanders, *Tetrahedron Lett.*, 1981, 4029; L.I. Kruse, C.W. DeBrosse, and C.H. Kruse, *J. Am. Chem. Soc.*, 1985, **107**, 5435 and references cited therein.

42. A. Murai, S. Sato, and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1982, 511.

43. U. Schubert, *Synthesis*, 1978, 364.

44. J.A. Marshall and R.H. Ellison, *J. Org. Chem.*, 1975, **40**, 2070.

45. M.S. Kablaoui, *J. Org. Chem.*, 1974, **39**, 3696.