Synthesis Based on Cyclohexadienes. Part 8.[1] Synthesis of 1-Methylbicyclo[2.2.2]oct-2-enecarboxylate Derivatives

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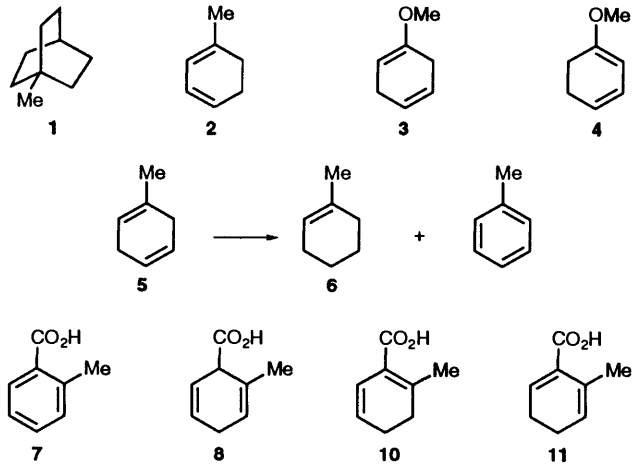
The 1,4-dihydrotoluic acids, obtained by the Birch reduction of 2-methyl- and 3-methyl-benzoic acids are isomerised to 2-methylcyclohexa-1,5-diene-1-carboxylic acid **10** and 5-methylcyclohexa-1,5-diene-1-carboxylic acid **15**, respectively. These conjugated diene acids undergo facile cycloaddition with dienophiles resulting in bicyclo[2.2.2]octene derivatives having a bridgehead methyl group. While the cycloaddition of **10** with dienophiles produces regioisomeric mixture of adducts, the acid **15** affords regiospecific products.

1-Methylbicyclo[2.2.2]octane **1** is an important structural subunit present in several naturally occurring sesquiterpenes, *e.g.*, khusiol, patchouli alcohol and seychellene. This structural moiety can be readily made from 1-methylcyclohexa-1,3-diene[2] by Diels–Alder reaction with an appropriate dienophile. However, preparation of **2** involves cumbersome procedures[3] and often results in isomeric diene mixtures. Birch reduction of anisole yields[4] 1-methoxycyclohexa-1,4-diene **3** which can be readily isomerised[5] to 1-methoxycyclohexa-1,3-diene **4**. Unlike

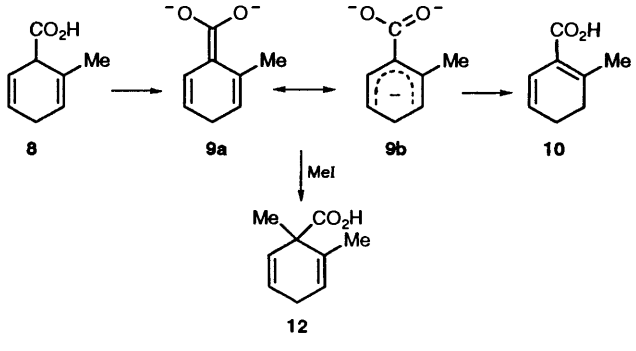


the diene **3**, base catalysed isomerisation of 1-methylcyclohexa-1,4-diene **5**, obtained by the metal–ammonia reduction of toluene, results[6] in disproportionation affording mainly toluene and 1-methylcyclohex-1-ene **6**. However, base catalysed isomerisation of 2-methylcyclohexa-2,5-diene-1-carboxylic acid **8**, obtained by the Birch reduction of 2-methylbenzoic acid, has been reported[7] to yield 2-methylcyclohexa-1,5-diene-1-carboxylic acid **10**. Decarboxylation[8] of **10** should result in the 1-methylcyclohexa-1,3-diene **2**. As part of our programme on the synthesis of tricyclic sesquiterpenes, we required an efficient method for the construction of the 1-methylbicyclo[2.2.2]octene framework and examined the base catalysed isomerisation of 1,4-dihydrotoluic acids and the Diels–Alder reaction of the resulting conjugated diene acids with various dienophiles to unravel the regiochemistry of the cyclic adducts and our results are reported in this paper.

(a) *Isomerisation of Dihydrotoluic Acids.*—Reduction of anisic and toluic acids with sodium in liquid ammonia was first examined by Birch[7] who observed that the carboxy group influenced the course of reduction of the benzene ring in these acids and that the hydrogens were added to the carbon bearing the carboxy group thus producing the 1,4-dihydro acids. Later Kuehne and Lambert[9] reported the formation of dihydro and tetrahydro acids during the sodium in liquid ammonia reduction of substituted benzoic acids and benzamides. They have further observed the hydrogenolysis of the methoxy group positioned *para* to the carboxy group in the reduction of 4-methoxybenzoic acid and 3,4,5-trimethoxybenzoic acid. Van Bekkum *et al.*,[10] thoroughly investigated the reduction of alkyl substituted benzoic acids with lithium in liquid ammonia and deduced a mechanism for the formation of the dihydro and tetrahydro acids.

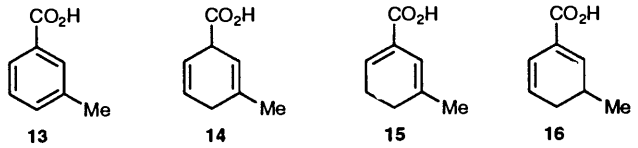
Reduction of 2-methylbenzoic acid **7** with sodium in liquid ammonia and quenching with ammonium chloride afforded the 2-methylcyclohexa-2,5-diene-1-carboxylic acid **8** in 95% yield. Similarly reduction of 3-methylbenzoic acid **13**, 4-methylbenzoic acid **17**, 2,3-dimethylbenzoic acid **20** and 2,5-dimethylbenzoic acid **23** gave 3-methylcyclohexa-2,5-diene-1-carboxylic acid **14**, 4-methylcyclohexa-2,5-diene-1-carboxylic acid **18**, 2,3-dimethylcyclohexa-2,5-diene-1-carboxylic acid **21a** and 2,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid **24a**, respectively, in excellent yields. The structures of these products were deduced from their ^{1}H NMR spectral data. Reduction using lithium did not improve the yield of the product.

The isomerisation of the dihydro acid **8** with 20% aqueous sodium hydroxide resulted in a mixture of the acids **7**, **8** and **10** from which the conjugated dihydro acid **10** was isolated in 15% yield. The conjugation of the acid **8** was investigated using other bases such as Bu^{t}OK–Bu^{t}OH, NaH–benzene, KNH_2–NH_3 and Bu^{t}OK–dimethyl sulfoxide (DMSO). In all these cases a mixture of products was obtained. However, treatment of the dihydro acid **8** with sodium methoxide in methanol afforded the conjugated acid **10**. The structure of the acid **10** was deduced from its spectral data, in particular the ^{1}H NMR spectrum showed two broad doublets at δ 5.7 and 6.4 for the two vicinal

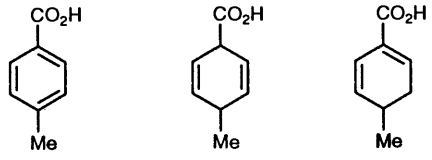


protons. The parent dihydro acid **8** exhibited resonances at δ 5.5 (1 H) and 5.8 (2 H), for the three olefinic protons as two broad singlets and a multiplet at δ 3.5 for the methine proton adjacent to the carboxy group. The isomeric structure **11** was excluded for the conjugated product on the basis of the ^{1}H NMR spectrum, since the olefinic proton situated β- to the carboxy group would have been deshielded and appeared at δ 6.8.

The mechanism of formation of the conjugated acid **10** from the acid **8** involves the base catalysed generation of the mesomeric anion **9a** which is in equilibrium with **9b** and its protonation. Kinetic protonation results in the unconjugated acid **8** while protonation under thermodynamic conditions affords the conjugated acid **10**. Protonation of the mesomeric anion **9a** can presumably occur at C-3 or C-5, leading to the compounds **10** and **11**, respectively, although experimental evidence indicates exclusive protonation at C-3. Methylation of the mesomeric anion **9a** has been shown[10] to produce 1,2-dimethylcyclohexa-2,5-diene-1-carboxylic acid **12**, the methyl group occupying the position adjacent to the carboxy group where the charge density would be maximum.



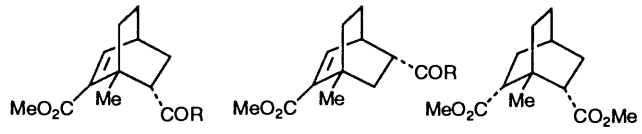
13 **14** **15** **16**



17 **18** **19**

Treatment of 3-methylcyclohexa-2,5-diene-1-carboxylic acid **14** with sodium methoxide in methanol afforded exclusively 5-methylcyclohexa-1,5-diene-1-carboxylic acid **15**. The ^{1}H NMR spectrum of the acid **15** indicated the presence of a methyl group at δ 2.2 and two olefinic protons, appeared as two broad doublets, at 5.7 and 6.4. From this data, the isomeric structure **16** for the conjugated product was ruled out. Isomerisation of the acid **18** with sodium methoxide in methanol produced the conjugated acid **19** in good yield. Conjugation of the acids **21a** and **24a** with sodium methoxide in methanol did not produce any of the desired material. However treatment of the methyl esters **21b** and **24b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene afforded the corresponding conjugated esters **22** and **25** in good yield. The structures were supported by their spectral data.

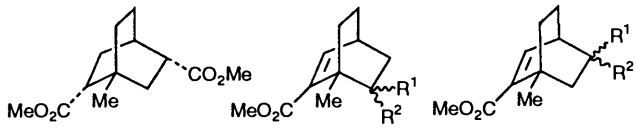
(b) *Diels–Alder Reactions.*—The conjugated acid **10** underwent cycloaddition smoothly with dienophiles resulting in a mixture of regioisomeric bicyclo[2.2.2]octene adducts. Treatment of the diene acid **10** with methyl acrylate in refluxing benzene, followed by esterification of the resulting product with ethereal diazomethane afforded a (2:1) mixture of adducts **26**



26 R = OMe
30 R = Me

27 R = OMe
31 R = Me

28



29

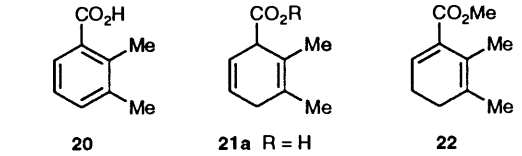
32 R^1 = Cl, R^2 = CN
34 R^1 = R^2 = O

33 R^1 = Cl, R^2 = CN
35 R^1 = R^2 = O

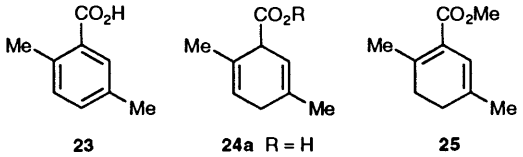
and **27**, easily separated by column chromatography. Compounds **26** and **27** were assumed to possess *endo* configuration (methoxycarbonyl group *endo* with respect to the double bond) from their ^{1}H NMR spectra. The ^{1}H NMR spectrum of **26** indicated the presence of an olefinic proton as a doublet at δ 7.13, two singlets due to the two methoxycarbonyl groups at δ 3.63 and 3.53, and a singlet at δ 1.4 due to the methyl group while that of the adduct **27** showed the olefinic proton at δ 7.0 as a doublet and the two methoxycarbonyl groups at 3.63 and 3.56 and the methyl group at 1.4 as singlets. Further confirmation of the structures of these products came from the hydrogenation experiments. The adduct **26** on catalytic hydrogenation produced the diester **28** having a planar symmetry as confirmed from its ^{13}C NMR spectrum, which showed 9 lines for the 13 carbon atoms. On the other hand, hydrogenation of **27** resulted in the product **29**, identical with the product obtained by the hydrogenation of the adduct **36** (see below) and showed 13 lines for the 13 carbon atoms as expected.

Similarly, the diene acid **10** when heated with methyl vinyl ketone and 2-chloroacrylonitrile afforded a mixture of adducts **30** and **31** and **32** and **33** in the ratio of (3:2) and (2:1), respectively. Hydrolysis of the mixture **32** and **33** with KOH–DMSO afforded the ketones **34** and **35**, which could be separated.

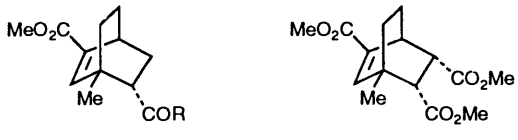
Unlike the diene acid **10**, cycloaddition of the conjugated acid **15** with a variety of dienophiles resulted in regiospecific products in good yield. Treatment of **15** with methyl acrylate followed by esterification gave the *endo*-dimethyl 4-methylbi-



20 **21a** R = H, **b** R = Me **22**

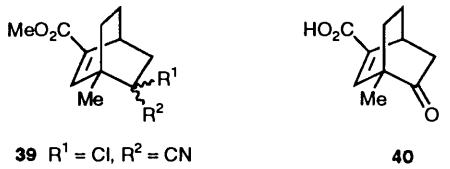


23 **24a** R = H, **b** R = Me **25**



36 R = OMe
37 R = Me

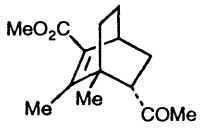
38



39 R^1 = Cl, R^2 = CN
41 R^1 = H, R^2 = CN

40

cyclo[2.2.2]oct-2-ene-2,5-dicarboxylate **36**. The ^{1}H NMR spectrum of **36** showed the presence of the olefinic proton as a doublet at δ 7.03, two singlets for the two methoxycarbonyl protons at 3.75 and 3.6 and a singlet at 1.24 for the methyl protons. Catalytic hydrogenation of **36** produced the unsymmetrical diester **29**, identical with the compound obtained from the adduct **27**, thus confirming its structure. Similarly, the adducts **37**, **38**, **39** and **41** were obtained from the cycloaddition of the conjugated diene acid **15** with the dienophiles, methyl vinyl ketone, maleic anhydride, 2-chloroacrylonitrile and acrylonitrile followed by esterification. In all the cases only *endo* adducts were obtained and these were characterised from their spectral data. Hydrolysis of the adduct **39** with KOH–DMSO produced the keto acid **40**. The adduct **41**, on oxidative decyanation[11] afforded the keto acid **40**, identical with the compound, obtained from the adduct **39**. Since the cycloaddition of the conjugated compound **19** produced bicyclo[2.2.2]octene derivatives without a bridgehead methyl group, this was not examined.



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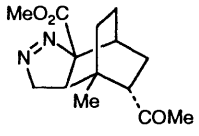

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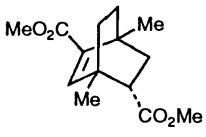
Treatment of the ester **22b** with methyl vinyl ketone produced the adduct **42** in good yield. The structure of the product was proved by comparison with an authentic product, obtained by the pyrolysis[12] of the pyrazolone **43**, readily prepared from the ester **37** with diazomethane. Cycloaddition of the ester **25b** with methyl acrylate afforded a (2:1) mixture of the regioisomeric adducts, **44** and **45**, which was separated and characterised.



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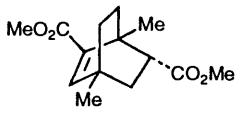

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In conclusion, a simple method for the regiospecific construction of bicyclo[2.2.2]octene derivatives having a bridgehead methyl group is described based on cycloaddition of 2-methylcyclohexa-1,5-diene-1-carboxylic acid **10** and 5-methylcyclohexa-1,5-diene-1-carboxylic acid **15** with dienophiles. While the cycloaddition of the acid **15** resulted in a single regiospecific adduct, a regioisomeric mixture of adducts was obtained with the acid **10**. The difference in the Diels–Alder regioselectivity between the acids **10** and **15** can be rationalised by frontier orbital considerations. It is clear from the above results that the methyl group appears to wield a superior directing effect with regard to the carboxy group in these cycloadditions.

Total synthesis of seychellene,[13] patchouli alcohol[14] and norpatchoulenol[14] has been achieved from the adducts **42** and **34**.

Experimental

Melting points were determined on a Mettler FP 1 instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 instrument as Nujol mulls. NMR spectra were recorded on Varian T-60 and JEOL FX 90Q spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. *J* Values are given in Hz. Mass spectra were taken on a JEOL DMX 303 instrument. Preparative TLC was carried out on 1 mm glass plates (20 × 20 cm) of Acme's silica gel. Acme's silica gel (60–120 mesh) was used for column chromatography. Liquid ammonia was distilled from sodium amide before use. The reaction mixtures were worked up by the addition of water followed by extraction with diethyl ether and then washing the organic phase successively with water, brine and water. The organic extracts were dried over anhydrous sodium sulfate. After removal of the solvent, the residues were purified either by preparative TLC or by column chromatography on silica gel and elution with hexane containing 5% ethyl acetate.

General Procedure for the Metal–Ammonia Reduction of Aromatic Carboxylic Acids.—The aromatic carboxylic acid in dry tetrahydrofuran (THF) was added to liquid ammonia with stirring. Sodium metal (4 equiv.) was then added in pieces until the reaction mixture attained a permanent blue colour. Stirring was continued for another 1 h. The mixture was then quenched by the addition of solid NH_4Cl in small portions until the solution became colourless. The ammonia was allowed to evaporate and then water was added to the residue and the aqueous solution was cooled and acidified with 10% hydrochloric acid. The reaction mixture was worked up as detailed before.

2-*Methylcyclohexa*-2,5-*diene*-1-*carboxylic acid* **8**. *o*-Toluic acid **7** (13.6 g, 100 mmol) in THF (150 cm^3) and liquid ammonia (1500 cm^3) was reduced with sodium (9 g) to yield the dihydro acid **8**, m.p. 76–77 °C (light petroleum) (lit.,[10] 77–78 °C). ν_{max}/cm^{-1} 3300–2300, 1695, 1650, 1310, 1220, 905, 780 and 680; δ 11.9 (s, 1 H, CO_2H), 5.8 (m, 2 H, C*H*=C*H*), 5.5 (m, 1 H, C*H*=C–CH_3), 3.5 (m, 1 H, CH), 2.8–2.4 (m, 2 H, CH_2) and 1.7 (s, 3 H, CH_3) (Found: C, 69.6; H, 7.3. Calc. for $C_8H_{10}O_2$: C, 69.5; H, 7.3%).

3-*Methylcyclohexa*-2,5-*diene*-1-*carboxylic acid* **14**. *m*-Toluic acid **13** (13.6 g, 100 mmol) was reduced with sodium (9 g) in liquid ammonia (1500 cm^3) to afford the dihydro acid **14**, m.p. 79–80 °C (light petroleum), (lit.,[10] 79.5–82.5 °C). ν_{max}/cm^{-1} 3300–2300, 1695, 1650, 1280, 1230, 940, 905 and 740; δ 11.5 (s, 1 H, CO_2H), 5.8 (m, 2 H, C*H*=C*H*), 5.4 (m, 1 H, *H*C=C–CH_3), 3.6 (m, 1 H, *H*CCO_2H), 2.5 (d, 2 H, *J* 8, CH_2) and 1.7 (s, 3 H, CH_3) (Found: C, 69.3; H, 7.5. Calc. for $C_8H_{10}O_2$: C, 69.5; H, 7.3%).

2,3-*Dimethylcyclohexa*-2,5-*diene*-1-*carboxylic acid* **21a**. 2,3-Dimethylbenzoic acid **20** (3 g, 20 mmol) was reduced with sodium (1.8 g) in THF (50 cm^3) and ammonia (500 cm^3) to afford the acid **21a**, m.p. 75–76 °C (light petroleum) (lit.,[10] 76 °C); ν_{max}/cm^{-1} 3300–2400, 1695, 1650, 1300, 1240, 900 and 695; δ 11.2 (s, 1 H, CO_2H), 5.8 (m, 2 H, C*H*=C*H*), 3.8 (m, 1 H, *H*CCO_2H), 2.8–2.5 (m, 2 H, CH_2) and 1.7 (s, 6 H, 2 × CH_3) (Found: C, 71.0; H, 7.9. Calc. for $C_9H_{12}O_2$: C, 71.1; H, 7.8%).

2,5-*Dimethylcyclohexa*-2,5-*diene*-1-*carboxylic acid* **24a**. 2,5-Dimethylbenzoic acid **23** (3 g, 20 mmol) in THF (50 cm^3) and ammonia (500 cm^3) was reduced with sodium (1.8 g). The reaction mixture was worked up to afford the acid **24a**, m.p. 81–82 °C (light petroleum) (lit.,[10] 83 °C); ν_{max}/cm^{-1} 3300–2400, 1690, 1305, 1220, 900 and 710; δ 11.9 (br, 1 H, CO_2H), 5.6 (m, 1 H, =CH), 5.4 (m, 1 H, =CH), 3.8–3.45 (m, 1 H), 2.75–2.24 (m, 2 H, CH_2) and 1.75 (s, 6 H, 2 × CH_3) (Found: C, 71.2, H, 7.8. Calc. for $C_9H_{12}O_2$, C, 71.1; H, 7.8%).

2-*Methylcyclohexa*-1,5-*diene*-1-*carboxylic acid* **10**. Conjugation of 2-methylcyclohexa-2,5-diene-1-carboxylic acid **8** (10 g, 72 mmol) gave the acid **10** in 95% yield, m.p. 75–76 °C (light petroleum) (lit.,[7] 76–78 °C). ν_{max}/cm^{-1} 3500–2300, 1685, 1630, 1590, 1270, 1080, 740 and 695; δ 11.8 (br s, 1 H, CO_2H), 6.5–6.2 (br d, 1 H, *H*C=CH), 5.9–5.5 (m, 1 H, HC=C*H*), 2.2 (s, 3 H, CH_3) and 2.4–1.7 (m, 4 H) (Found: C, 69.45; H, 7.2. Calc. for $C_8H_{10}O_2$: C, 69.54; H, 7.3%).

5-*Methylcyclohexa*-1,5-*diene*-1-*carboxylic acid* **15**. To a stirred solution of sodium methoxide (7.8 g, 145 mmol) in methanol (150 cm^3) was added 3-methylcyclohexa-2,5-diene-1-carboxylic

acid **14** (10 g, 72 mmol) in methanol (50 cm^3). The mixture was stirred at 70 °C for 5 h. The methanol was completely removed under reduced pressure. The white residue was dissolved in water (200 cm^3), cooled and acidified with 10% hydrochloric acid. The precipitate was filtered off and recrystallised from light petroleum, to afford the conjugated acid **15** (9.5 g, 95%), m.p. 95–96 °C. ν_{max}/cm^{-1} 3400–2250, 1685, 1650, 1605, 1290, 1180, 1100, 750 and 720; δ 11.8 (s, 1 H, CO_2H), 6.8 (m, 1 H, HC=C), 6.1 (m, 1 H, HC=C–CH_3), 2.5–2.1 (m, 4 H, 2 × CH_2) and 1.8 (s, 3 H, CH_3) (Found: C, 69.4; H, 7.4. $C_8H_{10}O_2$ requires C, 69.54; H, 7.3%).

Methyl 5,6-*dimethylcyclohexa*-1,5-*diene*-1-*carboxylate* **22**. A mixture of methyl 2,3-dimethylcyclohexa-2,5-diene-1-carboxylate **21b** (1.66 g, 10 mmol) and DBU (2.28 g, 15 mmol) in benzene (50 cm^3) was stirred at 70 °C for 5 h, and was then cooled and diluted with benzene (50 cm^3). The benzene solution was worked up to yield the conjugated ester **22** as a yellow oil (1.5 g, 90%); ν_{max}/cm^{-1} 1720, 1590, 1430, 1260, 1240, 1040 and 740; δ 6.6 (t, 1 H, HC=C), 3.6 (s, 3 H, CO_2CH_3), 2.1 (m, 4 H, 2 × CH_2) and 1.8 (s, 6 H, 2 × CH_3) (Found: C, 72.3; H, 8.4. $C_{10}H_{10}O_2$ requires C, 72.26; and H, 8.49%).

Methyl 2,5-*dimethylcyclohexa*-1,5-*diene*-1-*carboxylate* **25**. Conjugation of methyl 2,5-dimethylcyclohexa-2,5-diene-1-carboxylate **24b** (1.66 g, 10 mmol) with DBU yielded the product **25** (1.58 g, 95%); ν_{max}/cm^{-1} 1705, 1650, 1600, 1430, 1260, 1180 and 1060; δ 5.95 (s, 1 H, C=CH), 3.6 (s, 3 H, CO_2CH_3), 2.3–1.9 (m, 7 H, 2 × CH_2), 2.02 (s, 3 H, CH_3) and 1.8 (br s, 3-H, CH_3) (Found: C, 72.2; H, 8.4. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%).

General Procedure for Diels–Alder Reactions.—A benzene solution of diene, dienophile (excess) and hydroquinone (catalytic) was either refluxed or heated in a sealed tube in an oil bath. After completion, the reaction mixture was worked up by removal of the solvent and then the crude product was esterified with ethereal diazomethane. The crude ester was chromatographed on silica gel eluted with ethyl acetate–hexane (1:20) to afford the pure ester.

Dimethyl endo-1-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2,6-*dicarboxylate* **26** *and dimethyl* endo-1-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2,5-*dicarboxylate* **27**. The acid **10** (0.69 g, 5 mmol) and methyl acrylate (2.7 cm^3, 30 mmol) were heated at 120 °C for 48 h. The crude product was esterified and the mixture was chromatographed on silica gel. Elution with ethyl acetate–hexane (1:20) afforded the pure ester **26** (65%); ν_{max}/cm^{-1} 1740, 1710, 1610, 1430, 1260, 1205, 1160, 1080 and 755; δ 7.13 (d, 1 H, *J* 7, =CH), 3.63 (s, 3 H, CO_2CH_3), 3.53 (s, 3 H, CO_2CH_3), 2.83–2.53 (m, 1 H, bridgehead proton), 2.36 (dd, 1 H, *J* 10 and 6, C*H*CO_2Me), 1.4 (s, 3 H, CH_3), 2.1–1.15 (m, 6 H, 3 × CH_2) (Found: C, 65.6; H, 7.7. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%). Further elution with ethyl acetate–hexane (1:10) yielded the ester **27** (35%); δ 7.0 (d, 1 H, *J* 7, =CH), 3.63 (s, 3 H, CO_2CH_3), 3.56 (s, 3 H, CO_2CH_3), 3.3–2.9 (m, 1 H, bridgehead proton), 2.85–2.5 (m, 1 H), 1.4 (s, 3 H, CH_3) and 1.73–1.16 (m, 6-H, 3 × CH_2).

Dimethyl cis-1-*methylbicyclo*[2.2.2]*octane*-2,6-*dicarboxylate* **28**. Dimethyl *endo*-1-methylbicyclo[2.2.2]oct-2-ene-2,6-dicarboxylate **26** (100 mg) was hydrogenated to give the saturated diester **28** (95 mg, 95%); ν_{max}/cm^{-1} 1735, 1430, 1340, 1200, 1160, 1080 and 1030; δ 3.6 (s, 3 H, CO_2CH_3), 1.16 (s, 3 H, CH_3) and 2.6–1.36 (m, 10 H); ^{13}C NMR δ 174.8, 50.9, 45.1, 37.9, 33.5, 28.8, 25.1, 24.8 and 23.5 (Found: C, 64.9; H, 8.4. Calc. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.4%).

Dimethyl cis-1-*methylbicyclo*[2.2.2]*octane*-2,5-*dicarboxylate* **29**. The ester **27** (45 mg) in methanol (3 cm^3) was hydrogenated in the presence of 10% Pd–C catalyst (20 mg) until the hydrogen absorption ceased. The catalyst was filtered off and the solvent evaporated to afford the pure ester **29** (42 mg, 90%); ν_{max}/cm^{-1} 1735, 1460, 1440, 1370, 1200 and 1180; δ 3.64 (s, 3 H, CO_2CH_3), 3.58 (s, 3 H, CO_2CH_3), 2.7–1.3 (m, 10 H) and 0.76 (s, 3 H, CH_3); ^{13}C NMR δ 175.0 (s), 174.7 (s), 50.9 (q), 45.6 (d), 41.0 (d), 33.5 (t), 30.3 (s), 29.9 (t), 26.2 (d), 25.8 (t), 25.5 (t) and 24.8 (q) (Found: C, 64.9, H, 8.4. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%). Ester **29** was also obtained by hydrogenation of the dimethyl *endo*-4-methylbicyclo[2.2.2]oct-2-ene-2,5-dicarboxylate **36** (see below).

Methyl endo-6-*acetyl*-1-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2-*carboxylate* **30** *and methyl* endo-5-*acetyl*-1-*methylbicyclo*[2.2.2]-*oct*-2-*ene*-2-*carboxylate* **31**. The acid **10** (0.69 g, 5 mmol) and methyl vinyl ketone (4.16 cm^3, 50 mmol) were heated in a sealed tube at 100 °C for 36 h. The crude product was esterified to afford a mixture of regioisomers **30** and **31** (0.89 g, 80%). Purification by chromatography over silica gel and elution with ethyl acetate–hexane (1:20) afforded the ester **30** (0.5 g, 60%); ν_{max}/cm^{-1} 1715, 1705 and 1625; δ 7.1 (d, 1 H, *J* 7, =CH), 3.58 (s, 3 H, CO_2CH_3), 2.85–2.6 (m, 1 H, bridgehead proton), 2.5 (dd, 1 H, *J* 10, 6, C*H*$COCH_3$), 2.1–1.0 (m, 6 H, 3 × CH_2), 1.85 (s, 3 H, $COCH_3$) and 1.38 (s, 3 H, CH_3) (Found: C, 70.2; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%). Further elution with ethyl acetate–hexane (1:10) gave the pure ester **31** (0.2 g); ν_{max}/cm^{-1} 1710 and 1705; δ 6.95 (d, 1 H, *J* 7, =CH), 3.6 (s, 3 H, CO_2CH_3), 3.0–2.8 (m, 1 H), 1.92 (s, 3 H, $COCH_3$), 1.7–1.2 (m, 6 H) and 1.38 (s, 3 H, CH_3) (Found: C, 70.3; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

Methyl 6-*chloro*-6-*cyano*-1-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2-*carboxylate* **32** *and methyl* 5-*chloro*-5-*cyano*-1-*methylbicyclo*-[2.2.2]*oct*-2-*ene*-2-*carboxylate* **33**. The acid **10** (0.69 g, 5 mmol) and 2-chloroacrylonitrile (4 cm^3, 50 mmol) were heated at 100 °C for 36 h to afford the adduct which was esterified resulting in a mixture of regioisomers **32** and **33** (1 g, 84%). This mixture could not be separated even by chromatography. The mixture of **32** and **33** had, ν_{max}/cm^{-1} 2240, 1710 and 1610; δ 7.21, 7.26 (2 d, 2 × 1 H, *J* 7, =CH), 3.62, 3.65 (2 s, 2 × 3 H, CO_2CH_3), 1.65 (s, 2 × 3 H, CH_3) and 3.0–1.2 (m, 2 × 7 H).

Dimethyl endo-4-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2,5-*dicarboxylate* **36**. Treatment of the 5-methylcyclohexa-1,5-diene-1-carboxylic acid **15** (0.69 g, 5 mmol) with methyl acrylate (2.7 cm^3, 30 mmol) at 80 °C, in refluxing benzene for 12 h, afforded the diester **36** (1.025 g, 86%); ν_{max}/cm^{-1} 1740, 1710, 1630, 1440, 1280, 1255, 1075 and 755; δ 7.03 (s, 1 H, =CH), 3.75 (s, 3 H, CO_2CH_3), 3.6 (s, 3 H, CO_2CH_3), 3.24 (s, 1 H, bridgehead proton), 2.53 (dd, 1 H, *J* 10, 4, C*H*CO_2CH_3), 2.0–1.9 (m, 2 H, CH_2), 1.6–1.1 (m, 4 H, 2 × CH_2) and 1.24 (s, 3 H, CH_3) (Found: C, 65.5; H, 7.6. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%).

Methyl endo-5-*acetyl*-4-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2-*carboxylate* **37**. The acid **15** (0.69 g, 5 mmol) and methyl vinyl ketone (4.16 cm^3, 50 mmol) in benzene were refluxed for 24 h. The compound **37** (1.06 g, 96%) was obtained after esterification; ν_{max}/cm^{-1} 1715, 1705, 1625, 1435, 1280, 1250, 1155, 1070 and 760; δ 7.13 (s, 1 H, =CH), 3.75 (s, 3 H, CO_2CH_3), 3.26 (s, 1 H, bridgehead proton), 2.71 (dd, 1 H, *J* 10, 4, C*H*$COCH_3$), 2.1–1.94 (m, 2 H, CH_2), 2.02 (s, 3 H, $COCH_3$), 1.65–1.08 (m, 4 H, 2 × CH_2) and 1.23 (s, 3 H, $COCH_3$) (Found: C, 70.2; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

Trimethyl cis,endo-4-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2,5,6-*tricarboxylate* **38**.—The acid **15** (0.69 g, 5 mmol) and maleic anhydride (0.735 g, 75 mmol) were refluxed in benzene for 5 h and then the crude product was esterified. The compound **38** (1.4 g, 94%) was obtained as a pale-yellow liquid; ν_{max}/cm^{-1} 1740, 1710, 1620, 1190, 1040 and 775; δ 7.03 (s, 1 H, =CH), 3.79 (s, 3 H, CO_2CH_3), 3.59 (s, 3 H, CO_2CH_3), 3.54 (s, 3 H, CO_2CH_3), 3.12 (dd, 1 H, *J* 10, 2, *H*CHCO_2CH_3), 2.59 (d, 1 H, *J* 10, *H*CCO_2CH_3), 1.68–1.16 (m, 4 H, 2 × CH_2) and 1.26 (s, 3 H, CH_3) (Found: C, 60.8; H, 6.8. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%).

Methyl 5-*chloro*-5-*cyano*-4-*methylbicyclo*[2.2.2]*oct*-2-*ene*-2-*carboxylate* **39**. The acid **15** (0.69 g, 5 mmol) and 2-chloroacrylonitrile (4 cm^3, 50 mmol) were refluxed in benzene for 18 h.

After removal of benzene, the crude product was esterified to afford an epimeric mixture **39** (0.7 g, 73%) as a viscous liquid; ν_{max}/cm^{-1} 2240, 1710 and 1630; δ 6.8 (d, 1 H, *J* 2, =CH), 3.7 (s, 3 H, CO_2CH_3), 3.23 (m, 1 H, bridgehead proton) and 2.9–1.2 (m, 6 H, 3 × CH_2).

4-Methyl-5-oxobicyclo[2.2.2]*oct-2-ene-2-carboxylic acid* **40**. The above compound **39** was stirred in dimethyl sulfoxide (10 cm^3), with 20% aqueous potassium hydroxide (15 cm^3) at room temperature for 48 h. The reaction mixture was worked up to yield the keto acid **40** (0.45 g, 82%) which was crystallised from benzene–light petroleum (1:1), m.p. 143–145 °C; ν_{max}/cm^{-1} 3300–2600, 1710, 1690, 1615, 1450, 1300, 1290, 1090 and 750; δ 10.57–10.38 (br, 1 H, CO_2H), 7.08 (s, 1 H, =CH), 3.58 (br s, 1-H, bridgehead proton), 2.22–2.05 (m, 2 H, CH_2), 1.89–1.51 (m, 2 × CH_2) and 1.3 (s, 3 H, CH_3); ^{13}C NMR δ 211.4 (s), 168.6 (s), 145.9 (d), 138.8 (s), 50.9 (s), 39.2 (t), 31.3 (d), 30.1 (t), 25.5 (t) and 16.9 (q) (Found: C, 66.6; H, 6.7. $C_{10}H_{12}O_3$ requires C, 66.6; H, 6.7%).

Methyl 5-cyano-4-*methylbicyclo*[2.2.2]*oct-2-ene-2-carboxylate* **41**. The acid **15** (0.69 g, 5 mmol) and acrylonitrile (1.3 cm^3, 20 mmol) were refluxed at 80 °C for 48 h. Removal of the solvent followed by esterification gave the ester **41** (0.98 g, 96%) as a pale-yellow liquid; ν_{max}/cm^{-1} 2245, 1715, 1625, 1440, 1280, 1065 and 760; δ 6.9 (s, 1 H, =CH), 3.7 (s, 3 H, CO_2CH_3), 3.23 (m, 1 H, bridgehead proton), 2.56 (dd, 1 H, *J* 10, 4, CHCN), 2.3–1.83 (m, 2 H, CH_2), 1.76–1.06 (m, 4 H, 2 × CH_2) and 1.46 (s, 3 H, CH_3) (Found: C, 70.2; H, 7.3; N, 15.5. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 15.6%).

Methyl endo-5-*acetyl*-3,4-*dimethylbicyclo*[2.2.2]*oct-2-ene-2-carboxylate* **42**. The diene ester **22** (0.88 g, 5 mmol) and methyl vinyl ketone (4.2 cm^3, 50 mmol) were heated in a sealed tube at 80 °C, for 12 h, and the product was esterified to afford the ester **42** (1.025 g, 82%); ν_{max}/cm^{-1} 1700 and 1610; δ 3.66 (s, 3 H, CO_2CH_3), 3.3–3.06 (m, 1 H, bridgehead proton), 2.58 (dd, 1 H, *J* 10, 6, C*H*$COCH_3$), 2.2 (s, 3 H, CH_3), 2.33–0.66 (m, 6 H), 1.96 (s, 3H, CO_2CH_3) and 1.16 (s, 3H, CH_3) (Found: C, 71.1; H, 8.6%; M^+, 236.1404. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%; *M*, 236.1412).

Pyrazoline derivative **43**. Methyl *endo*-5-acetyl-4-methylbicyclo[2.2.2]oct-2-ene-2-carboxylate **37** (6.66 g, 30 mmol) in chloroform (20 cm^3) was treated with an ethereal solution of diazomethane (large excess) in a stoppered flask protected from light, and left at 4 °C until the reaction was complete (7 days) as monitored by TLC. The reaction mixture was worked up to afford the pyrazoline derivative **43** (7.8 g, 98.5%) as a viscous liquid; ν_{max}/cm^{-1} 1725, 1700 and 1550; δ 4.76 (dd, 1 H, *J* 18, 4, NCH), 4.3 (dd, 1 H, *J* 18, 8, NCH), 3.7 (s, 3 H, CO_2CH_3), 3.1–0.9 (m, 9 H, 3 × CH_2 and 3 × CH), 2.1 (s, 3 H, $COCH_3$), 0.83 (s, 3 H, CH_3); ^{13}C NMR δ 211.58 (s), 169.17 (s), 101.23 (s), 80.25 (t), 52.6 (d), 52.4 (q), 35.67 (d), 32.76 (s), 32.5 (q), 28.62 (d), 27.74 (t), 27.37 (t), 23.18 (q) and 20.37 (t) (Found: M^+, 264.1475. Calc. for $C_{14}H_{20}N_2O_3$: *M*, 264.1474).

The above pyrazoline derivative **43** (5.0 g) was heated in ethylene glycol (10 cm^3) at 200 °C for 15 min. The product was worked up to afford the ester **42** (3.75 g, 80%), identical with the above.

Dimethyl endo-1,4-*dimethylbicyclo*[2.2.2]*oct-2-ene-2,5-dicarboxylate* **44** *and dimethyl* endo-1,4-*dimethylbicyclo*[2.2.2]*oct-2-ene-2,6-dicarboxylate* **45**. The diene ester **25** (0.88 g, 5 mmol) and methyl acrylate (2.7 cm^3, 30 mmol) were heated in a sealed tube at 120 °C, for 48 h. The reaction mixture was esterified to yield the diester as a mixture of regioisomers **44** and **45** (1.015 g, 76%) in 2:1 ratio which resisted separation. The mixture had ν_{max}/cm^{-1} 1730, 1715 and 1600; δ 6.93, 6.83 (2 s, 2 × 1 H, =CH), 3.66, 3.65 (2 s, 2 × 1 H, *J* 10, 6, C*H*CO_2CH_3), 3.61, 3.6 (2 s, 2 × 3 H, CO_2CH_3), 2.5, 2.4 (2 dd, 2 × 1 H, *J* 10, 6, C*H*CO_2CH_3), 2.0–0.9 (m, 2 × 6 H), 1.4, 1.36 (2 s, 2 × 3 H, CH_3), 1.23 and 1.2 (2 s, 2 × 3 H, CH_3) (Found: C, 66.6, H, 7.9, $C_{14}H_{20}O_4$ requires C, 66.6; H, 8.0%).

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References

1 Part 7, S. Raghavan and G. S. R. Subba Rao, *Heterocycles*, 1993, in the press.
2 R. P. Gregson and R. N. Mirrington, *Aust. J. Chem.*, 1976, **29**, 2037.
3 A. J. Birch and G. S. R. Subba Rao, *Aust. J. Chem.*, 1970, **23**, 1641.
4 A. J. Birch, E. M. A. Shouky and F. Stansfield, *J. Chem. Soc.*, 1961, 5376.
5 A. J. Birch and G. S. R. Subba Rao, *Adv. Org. Chem.*, 1972, **8**, 1–65.
6 A. J. Birch, *J. Chem. Soc.*, 1947, 1642.
7 A. J. Birch, *J. Chem. Soc.*, 1950, 1551.
8 D. H. R. Barton, H. Togo and S. Z. Zard, *Tetrahedron*, 1985, **41**, 5507.
9 M. E. Kuehne and B. F. Lambert, *J. Am. Chem. Soc.*, 1959, **81**, 4278.
10 H. Van Bekkum, C. B. Van Den Bosch, G. Van Minnenpathuis, J. C. DeMos and A. M. Van Wijk, *Recl. Trav. Chim. Pays-Bas*, 1971, **90**, 137.
11 R. W. Freerksen, S. J. Selikson, R. B. Wroble, K. S. Kyler and D. S. Watl, *J. Org. Chem.*, 1983, **48**, 4087.
12 C. Cariviela, M. D. Diaz de Villegas, J. A. Mayoral and E. Melendez, *J. Org. Chem.*, 1985, **50**, 3167.
13 K. V. Bhaskar and G. S. R. Subba Rao, *Tetrahedron Lett.*, 1989, 225.
14 G. S. R. Subba Rao and K. Kaliappan, unpublished work.

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