Methyl 2-aryl-2*H*-azirine-3-carboxylates as dienophiles

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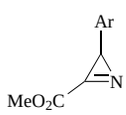
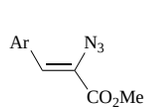
Diels–Alder reactions of the methyl 2-aryl-2*H*-azirine-3-carboxylates 1a and 1b have been investigated in order to determine the stereoselectivity and regioselectivity of the reaction. The azirines react with a range of electron rich dienes at room temperature to give Diels–Alder adducts. The reaction leads to the formation of *endo*-cycloadducts with both cyclic and acyclic dienes; furan is exceptional in giving an *exo*-adduct 7. X-Ray crystallography has established the structure 9 of the Diels–Alder adduct formed from the azirine 1a and 1-acetoxybutadiene. The same regioselectivity, in which the more nucleophilic terminus of the diene combines with the carbon atom of the C=N bond, is found in the adducts from several other 1- and 2-substituted dienes. Only isoprene, among the dienes examined, gives a mixture containing the opposite regioisomer 14 as a minor component.

The hetero Diels–Alder reaction has become an important method of synthesis of six-membered heterocycles.[1] The range of useful dienophiles that incorporate a C=N bond is nevertheless rather limited. Intermolecular reactions are largely restricted to iminium cations and to imines bearing at least one, and usually two, electron withdrawing substituents.[2] We wished to exploit the strained double bond of the 2*H*-azirine ring system in cycloaddition reactions. The analogously strained cyclopropenes participate well in Diels–Alder reactions even when there are no activating substituents attached to the carbon–carbon double bond.[3] By comparison there are relatively few examples of Diels–Alder reactions of 2*H*-azirines.[2,4]

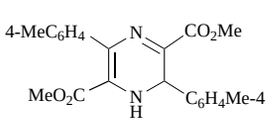
In a preliminary investigation we explored the potential of 2-aryl-2*H*-azirine-3-carboxylic esters **1** to act as dienophiles, this



1a Ar = C_6H_4Me-4
b Ar = $C_6H_3Cl_2$-2,6
c Ar = C_6H_4Cl-4



2a Ar = C_6H_4Me-4
b Ar = $C_6H_3Cl_2$-2,6



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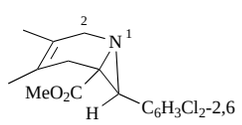

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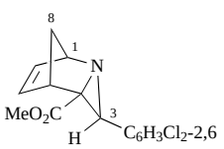

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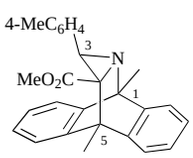

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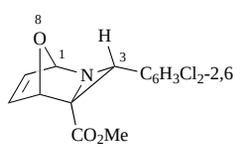

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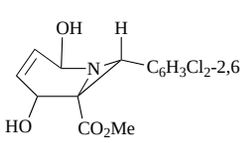

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being based on the assumption that a combination of a strained C=N bond and an electron withdrawing group would result in high reactivity. This indeed proved to be the case with three dienes.[5] We describe here the results of a more extensive investigation of this reaction which was designed to delineate the scope and the selectivity of the process.

The 2*H*-azirines **1** were prepared by thermolysis of the corresponding α-azidopropenoic esters **2** in heptane.[6,7] The progress of the reaction must be carefully monitored because at higher temperatures or with long reaction times other products, particularly indole-2-carboxylates,[7] predominate. A similar route to 2-alkylazirine-3-carboxylates has been described[8] but the other standard route to 2*H*-azirines, the Neber rearrangement of oxime toluene-*p*-sulfonates, has not been used to produce azirines of this type. Another literature route, with few examples, is the reaction of phosphonium ylides with ethyl chloroformate oxime.[9] Our investigation has been restricted to the two azirine esters **1a** and **1b**, the 2,6-dichlorophenyl derivative **1b** being the more stable. The 2,6-dichlorophenylazirine **1b** was obtained pure and crystalline whereas the 4-tolylazirine **1a** was always contaminated with a small amount (*ca.* 10%) of methyl 6-methylindole-2-carboxylate. Both azirines react very easily with nucleophiles and **1a** did not survive extended column chromatography on silica. The major product obtained from the column was the dihydropyrazine **3**, which is a dimer of the azirine.

The dienes, chosen to test the reactivity of the azirines and the regioselectivity and *endo*:*exo* selectivity of the cycloaddition, were mixed with the azirines in dry diethyl ether or dry THF at room temperature and the reaction mixtures were monitored by TLC until no further change could be detected. Readily available and volatile dienes, including furan and 2,3-dimethylbutadiene, were used in large excess, but others were used in equimolar amounts or a small excess and this did not significantly diminish the yields of the reaction products.

Reactions with symmetrical dienes

We have described the reaction of crude samples of azirines **1a** and **1c** with 2,3-dimethylbutadiene and with cyclopentadiene. Analogous reactions of a purified sample of the azirine **1b** with these dienes gave the expected cycloadducts **4** (40%) and **5** (65%). The addition to cyclopentadiene is *endo*; this is indicated in particular by the shielding of the aziridine ring hydrogen H-3 in the ^1H NMR spectrum caused by interaction with the carbon–carbon double bond. The signal appears at δ 2.65 in **5** but typically at δ 3.0–3.5 in adducts with acyclic dienes. Similar shielding effects have been observed in *endo*-adducts of cyclopentadiene with cyclopropenes.[10] Anthracene did not give a cycloadduct with the azirine **1a** after 7 days at room temperature followed by heating at 50 °C for 10 h but the more electron

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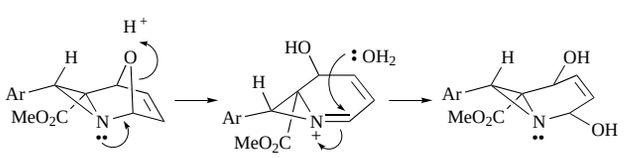
rich 9,10-dimethylanthracene gave the expected adduct **6** (60%) after 7 days at room temperature. The signal for the aziridine ring hydrogen is at δ 2.07 in this adduct because of shielding by the benzene ring.

The azirine **1b** reacted with furan at room temperature. The adduct was obtained in quantitative yield by dissolving the azirine in a mixture of diethyl ether and furan, leaving the solution for 7 days at room temperature, then removing the diethyl ether and the excess furan. The residual oil slowly crystallised to give a solid, mp 64–66 °C, that analysed correctly for a 1 : 1 adduct. The NMR spectrum is distinctly different from those of the other azirine adducts. In particular, the signal for the aziridine ring hydrogen (H-3) appears at δ 3.89. It has been assigned the *exo* structure **7** on the basis that H-3 is deshielded by the adjacent oxygen atom.

In contrast to the compounds described above, the furan adduct proved to be extremely unstable and difficult to handle. The low stability of the adduct may be due in part to the antiperiplanar disposition of the nitrogen lone pair and a bridgehead C–O bond, which will favour cleavage of the bond. When a drop of water was added to the furan adduct **7** at room temperature it was rapidly and cleanly converted into a new compound that contained the elements of an extra molecule of water. This compound has been assigned the structure **8** on the basis of its ^{1}H NMR spectrum. Signals in the spectrum at δ 5.62 and 5.85 have been assigned respectively to H-5 and H-2. Both show small couplings: the signal at δ 5.62 is a triplet (J 1.6 Hz) and that at δ 5.85 appears as a broadened singlet in the 400 MHz spectrum. A signal at δ 6.04, assigned to H-3, is coupled to H-4, H-5 and H-2 with coupling constants, J, of 6.0, 1.6 and 1.2 Hz and a signal at δ 6.09, assigned to H-4, is coupled to H-3, H-5 and H-2 with coupling constants of J 6.0, 1.6 and 0.6 Hz. The small coupling constants indicate that H-2 and H-5 are in similar environments and that both are in pseudo-axial positions in the boat-like six membered ring. This structure is consistent with opening of the bridgehead ether linkage, assisted by the nitrogen lone pair, followed by capture of the iminium cation by water from the same face. The attack on this face is required for stereoelectronic reasons, to allow the nitrogen lone pair to develop on the opposite face and thus minimise strain in the bicyclic product (Scheme 1).



Scheme 1

Cyclopropenes are known to react with furan to give *exo*-cycloadducts predominantly or exclusively.[3] Some workers have considered that steric effects may explain this preference.[11] However, it is known that *exo*-adducts are isolated from the reaction of furan with other dienophiles because the Diels–Alder reactions are reversible, and the products result from thermodynamic control.[12] Compound **7** is the first example of a Diels–Alder adduct of furan and a 2*H*-azirine, although adducts of 1,3-diphenylisobenzofuran have been described earlier.

Reactions with unsymmetrical dienes

This series of reactions was carried out with a range of acyclic dienes in order to determine the regioselectivity and the *endo* : *exo* selectivity of the cycloaddition. The azirine **1a** reacted with 1-acetoxybutadiene at room temperature and gave a crystalline adduct which is formulated as **9** on the basis of an X-ray structure determination (Fig. 1). Selected bond lengths and bond angles are listed in Table 1. The structure is consistent with *endo* addition of the azirine to (*E*)-1-

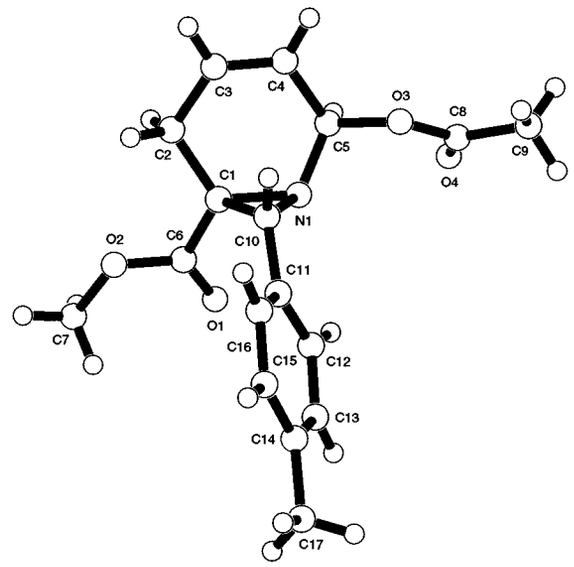


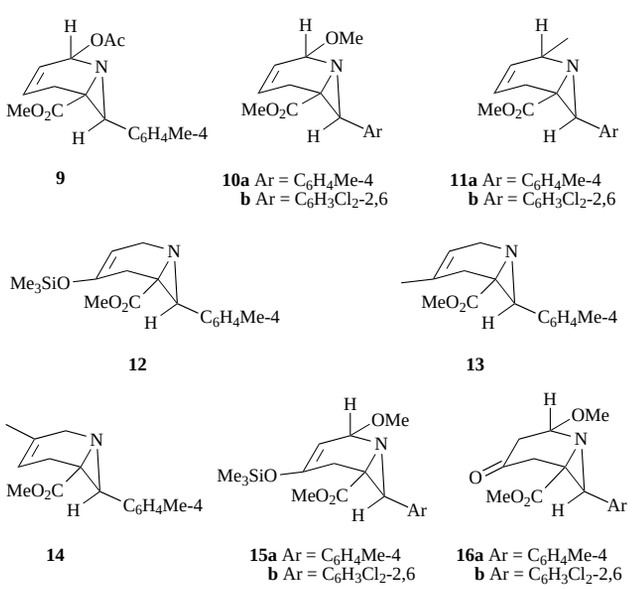
Fig. 1 X-Ray crystal structure of the aziridine **9**

Table 1 Selected bond lengths and bond angles for **9**[a]

Bond lengths (Å)		Bond angles (°)	
N1–C1	1.482(8)	C1–N1–C10	61.5(4)
N1–C10	1.478(7)	N1–C1–C10	59.1(4)
N1–C5	1.430(8)	C1–C10–N1	59.4(4)
C1–C10	1.512(8)	N1–C10–C11	119.0(5)
C1–C2	1.548(8)	N1–C5–C4	117.2(5)
C2–C3	1.457(9)	C1–C2–C3	112.3(6)
C3–C4	1.306(9)	C2–C3–C4	124.6(6)
C4–C5	1.534(9)	C3–C4–C5	119.5(6)

[a] Atom numbering corresponds to that in Fig. 1.

acetoxybutadiene. There was no evidence for the presence of any isomeric adducts in the crude reaction mixture. The ^{1}H and ^{13}C NMR spectra of structure **9** show features that proved also



to be present in other adducts formed from the azirines with unsymmetrical dienes and which are therefore useful in establishing their structure. The assignments are shown in Fig. 2. A COSY spectrum revealed cross-ring coupling between H-2 and H-5$_\beta$; H-2 is also weakly coupled to H-3 and H-4.

Two other dienes, 1-methoxybutadiene and penta-1,3-diene, were investigated. Both dienes reacted readily with the azirines **1a** and **1b** at room temperature. In each case a single cycload-

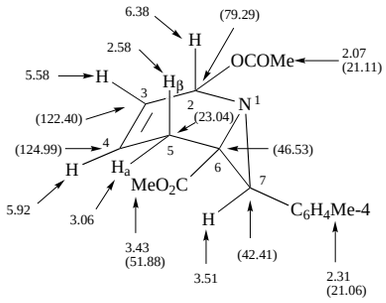


Fig. 2 Assignment of chemical shifts for the ^{1}H NMR spectrum and the ^{13}C NMR spectrum (in parentheses) of compound **9**

duct was isolated. The structures **10a**,**b** and **11a**,**b** were assigned to these compounds, mainly on the basis of a comparison of their ^{13}C and ^{1}H NMR spectra with those of the aziridine **9**.

The regioselectivity of addition to two 2-substituted dienes, 2-trimethylsilyloxybuta-1,3-diene and isoprene, was also determined. The azirine **1a** gave the aziridine **12**, an oil, as the only detectable regioisomer when it was reacted with 2-trimethylsilyloxybuta-1,3-diene at room temperature. The structural assignment is based on the NMR spectra; in particular, there is no vicinal coupling to the hydrogen atoms attached to C-5. The azirine **1a** and isoprene gave an oil that was not fully characterised but which was clearly a mixture of isomers on the basis of its NMR spectrum. There are two unresolved multiplets in the spectrum centred at δ 5.27 and 5.46 in the ratio 2.7 : 1 which have been assigned respectively to H-3 in structure **13** and to H-4 in structure **14** since the chemical shift of H-4 is larger than that of H-3 in all the symmetrical adducts.

The unsymmetrical diene 1-methoxy-3-trimethylsilyloxybuta-1,3-diene reacted readily with both the azirines **1a** and **1b**. Two products were isolated from each reaction mixture by flash column chromatography. The major products were assigned the silyl ether structures **15a**,**b** on the basis of accurate mass measurements (**15a**) and their ^{1}H NMR spectra, which were assigned by comparison of characteristic signals with those in **10a**,**b** and **12**. These compounds are both oils and neither were obtained completely pure. The NMR spectra of both compounds show the presence of other minor components (<10%) which were not identified. The other products isolated from the reaction mixtures were the corresponding ketones **16a**,**b** which we assume were formed by loss of the trimethylsilyl group during chromatography. The silyl ether **15b** was converted into the ketone **16b** (94% isolated yield) when a solution was stirred with silica for 19 h. These ketones are crystalline solids and both were fully characterised.

Conclusions

The azirine esters **1a** and **1b** have been shown to react with a variety of electron rich dienes at room temperature. The cycloadditions are *endo* selective, except with furan, and the reactions consistently show the same regioselectivity of addition in which the more nucleophilic terminus of the diene combines with the carbon atom of the C=N bond. The products are fused aziridine esters of a type that has not previously been reported. The Diels–Alder reactions should be capable of extension to other activated azirines.

Experimental

General

^{1}H NMR spectra were recorded either on a Bruker AC 200 (200 MHz), on a Varian Gemini 2000 (300 MHz) or on a Bruker AMX 400 (400 MHz) spectrometer. Multiplicities are recorded as broad peaks (b), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). *J* Values are in Hz. Infrared spectra were recorded either on a Perkin-Elmer 298 or on a Perkin-Elmer 1720-X FTIR spectrometer. Solid samples were run as Nujol mulls, and liquids as thin films. Mass spectra were recorded on a VG Micromass 7070E machine as electron impact spectra (70 eV). Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. Melting points (mp) were determined on a Kofler block. Dry column flash chromatography[13] was carried out using Kieselgel 60 and water pump vacuum. Thin layer chromatography (TLC) was carried out on Merck 10 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}.

Methyl 2-azido-3-(4-methylphenyl)propenoate 2a and methyl 2-azido-3-(2,6-dichlorophenyl)propenoate 2b

The azido esters were prepared (80 and 73% respectively) from methyl azidoacetate and the appropriate aldehyde, using the conditions described by Henn *et al.*[7]

Methyl 2-(4-methylphenyl)-2*H*-azirine-3-carboxylate 1a

A solution of the ester **2a** (1.19 g, 5.48 mmol) in heptane (20 ml) was heated under reflux for 3 h, when all the starting ester had decomposed (TLC). The solution was evaporated to leave the azirine **2a** (0.83 g, 80%) as an oil, which was converted into a yellow solid after trituration with diethyl ether–hexane; δ_H(300 MHz) 3.46 (H-3). The ^{1}H NMR spectrum showed signals attributable to methyl 6-methylindole-2-carboxylate as an impurity (*ca.* 10%).

Dimethyl 2,5-bis(4-methylphenyl)-1,2-dihydropyrazine-3,6-dicarboxylate 3

An attempt was made to purify the crude azirine **1a**, prepared as described above, by flash column chromatography. Elution with diethyl ether gave methyl 6-methylindole-2-carboxylate (0.1 g) followed by the dihydropyrazine **3** as an orange solid (0.12 g), mp 138–140 °C (from diethyl ether) (Found: C, 69.9; H, 5.9; N, 7.4. $C_{22}H_{22}N_2O_4$ requires C, 69.8; H, 5.9; N, 7.4%); ν_{max}(Nujol)/cm^{-1} 3356, 3311, 1729 and 1714; δ_H(300 MHz) 2.27 (3 H, s), 2.32 (3 H, s), 3.62 (3 H, s), 3.92 (3 H, s), 5.86 (1 H, bs, NH), 5.92 (1 H, d, *J* 5.5, H-2), 7.03–7.14 (6 H, m) and 7.61 (2 H, d, *J* 8.0); δ_C(75.5 MHz) 20.94, 21.12, 49.52 (C-2), 52.32, 52.89, 121.63, 126.09, 126.38, 128.53, 129.30, 133.92, 134.22, 134.56, 135.11, 137.29, 137.99, 164.78 and 164.95; *m*/*z* 378 (M^+, 70%) and 237 (100). After 15 days in solution the sample gave a ^{13}C NMR spectrum consistent with that expected for the aromatic pyrazine, dimethyl 3,6-bis(4-methylphenyl)pyrazine-2,5-dicarboxylate; δ_C 21.80, 52.96, 128.64, 129.53, 133.14, 140.35, 144.30, 149.46 and 166.82.

Methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate 1b

A solution of the ester **2b** (1.04 g, 3.82 mmol) in heptane (25 ml) was heated under reflux for 2 h, when all the starting ester had decomposed (TLC). The solution was evaporated to leave the azirine **2b** (0.81 g, 87%), mp 52–54 °C (from light petroleum bp 40–60 °C) (lit.,[6] 69–71 °C); ν_{max}(Nujol)/cm^{-1} 1761 and 1723; δ_H(300 MHz) 3.62 (1 H, s, H-3), 4.06 (3 H, s) and 7.15–7.31 (3 H, m).

Diels–Alder reactions. General procedure

The azirine (0.2–0.3 g) was dissolved in dry THF or dry diethyl ether (3–4 ml) and to this was added the diene in large excess (2,3-dimethylbutadiene, cyclopentadiene, furan, penta-1,3-diene and isoprene) or 1–2 equiv. (other dienes). The solution was left at room temperature for periods ranging from a few min to several days, until the azirine could no longer be detected by TLC. The solvent was then removed. In reactions with furan, cyclopentadiene and 1-methoxybutadiene the products were purified by crystallisation; in other cases they were isolated by flash column chromatography using mixtures of hexane and diethyl ether as the eluent. The following compounds were isolated.

Methyl 7-(2,6-dichlorophenyl)-3,4-dimethyl-1-azabicyclo-[4.1.0]hept-3-ene-6-carboxylate 4. Isolated in 40% yield after 24 h, mp 112–113 °C (from diethyl ether–hexane) (Found: C, 58.9; H, 5.25; N, 4.3. $C_{16}H_{17}Cl_2NO_2$ requires C, 58.9; H, 5.2; N, 4.3%); ν_{max}(Nujol)/cm^{-1} 1714; δ_H(300 MHz) 1.62 (3 H, s), 1.74 (3 H, s), 2.83 (2 H, s, H-5), 3.19 (1 H, s, H-7), 3.43 (3 H, s), 3.70 (1 H, d, *J* 17.5, H-2), 3.80 (1 H, d, *J* 17.5, H-2), 7.10 (1 H, t, *J* 8.2) and 7.26 (2 H, d, *J* 8.2); δ_C(75.5 MHz) 16.47, 18.75, 28.37, 42.98, 45.91, 52.10, 119.48, 121.55, 128.05, 128.35, 128.53, 133.80, 138.19 and 171.89; *m*/*z* 325, 327 and 329 (M^+).

***endo*-Methyl 3-(2,6-dichlorophenyl)-2-azatricyclo[3.2.1.0^{2,4}]-oct-6-ene-4-carboxylate 5.** Isolated in 65% yield after 2 h, mp 105–106 °C (from diethyl ether–hexane) (Found: C, 58.1; H, 4.3; N, 4.4. $C_{15}H_{13}Cl_2NO_2$ requires C, 58.1; H, 4.2; N, 4.5%); ν_{max}(Nujol)/cm^{-1} 1723; δ_H(400 MHz) 1.82 (1 H, d, *J* 8.3, H-8), 2.04 (1 H, dt, *J* 8.3 and 2.0, H-8), 2.65 (1 H, s, H-3), 3.50 (3 H, s), 3.89–3.91 (1 H, m, H-5), 4.45–4.48 (1 H, m, H-1), 5.86 (1 H, ddd, *J* 5.4, 2.5 and 0.7, H-7), 6.37 (1 H, ddd, *J* 5.4, 3.6 and 1.7, H-6), 7.09 (1 H, t, *J* 7.9) and 7.23 (2 H, d, *J* 7.9); *m*/*z* 309, 311 and 315 (M^+).

Methyl 1,8-dimethyl-16-(4-methylphenyl)-15-azapentacyclo-[6.6.3.0^{2,7}.0^{9,14}.0^{15,17}]heptadeca-2(7),3,5,9(14),10,12-hexaene-17-carboxylate 6.‡ Isolated in 60% yield after 7 days, mp 137–138 °C (from diethyl ether–hexane) (Found: C, 81.8; H, 6.4; N, 3.4. $C_{27}H_{25}NO_2$ requires C, 82.0; H, 6.4; N, 3.5%); ν_{max}(Nujol)/cm^{-1} 1743 and 1727; δ_H(300 MHz) 2.07 (1 H, s, H-3), 2.08 (3 H, s), 2.24 (3 H, s), 2.45 (3 H, s), 3.29 (3 H, s), 6.98 (2 H, d, *J* 8.6), 6.99 (2 H, d, *J* 8.6) and 7.15–7.55 (8 H, m); δ_C(75.5 MHz) 15.05, 17.49, 21.05 (Ar-Me), 44.51 (C-4), 48.28 (C-3), 51.48 (OMe), 58.91 (C-5), 61.80 (C-1), 121.51, 121.59, 122.06, 125.97, 126.25, 127.01, 127.08, 127.15, 128.64, 133.93, 136.72, 140.03, 140.52, 143.78, 145.15 and 168.79; *m*/*z* 395 (M^+).

Methyl 3-(2,6-dichlorophenyl)-8-oxa-2-azatricyclo[3.2.1.0^{2,4}]-oct-6-ene-4-carboxylate 7. Isolated in 100% yield after 7 days, mp 64–66 °C (from diethyl ether) (Found: C, 53.6; H, 3.6; N, 4.5. $C_{14}H_{11}Cl_2NO_3$ requires C, 53.9; H, 3.55; N, 4.5%); ν_{max}(film)/cm^{-1} 1750 and 1723; δ_H(300 MHz) 3.12 (3 H, s), 3.89 (1 H, s, H-3), 5.22 (1 H, d, *J* 1.5, H-5), 5.39 (1 H, bs, H-1), 6.17 (1 H, dd, *J* 5.7 and 1.5, H-7), 6.45 (1 H, dd, *J* 5.7 and 1.2, H-6), 6.49 (1 H, t, *J* 8.1) and 6.92 (2 H, d, *J* 8.1); δ_C(75.5 MHz) 50.99 (C-3), 51.20 (OMe), 54.00 (C-4), 76.75 (C-5), 93.09 (C-1), 128.00, 128.45, 132.40, 135.95, 137.43, 137.90 and 169.20, *m*/*z* (CI) 312 [$(M + H)^+$].

Methyl 2-acetoxy-7-(4-methylphenyl)-1-azabicyclo[4.1.0]-hept-3-ene-6-carboxylate 9. Isolated in 48% yield after 60 h, mp 100.5–101.5 °C (from diethyl ether–hexane) (Found: C, 68.0; H, 6.4; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.35; N, 4.65%); ν_{max}(Nujol)/cm^{-1} 1748; δ_H(400 MHz) 2.07 (3 H, s), 2.31 (3 H, s), 2.58 (1 H, ddd, *J* 19.2, 5.3 and 2.3, H-5$_\beta$), 3.06 (1 H, dd, *J* 19.2 and 6.0, H-5$_\alpha$), 3.43 (3 H, s), 3.51 (1 H, s, H-7), 5.58 (1 H, dm, *J* 10.5, H-3), 5.92 (1 H, ddt, *J* 10.5, 6.0 and 2.3, H-4), 6.37–6.38 (1 H, m, H-2), 7.16 (2 H, d, *J* 7.9) and 7.24 (2 H, d, *J* 7.9); δ_C(75.5 MHz) 21.06, 21.11, 23.04, 42.41, 46.53, 51.88, 79.29, 122.40, 124.99, 127.42, 128.72, 132.51, 137.03, 169.64 and 169.96; *m*/*z* 301 (M^+).

Methyl 2-methoxy-7-(4-methylphenyl)-1-azabicyclo[4.1.0]-hept-3-ene-6-carboxylate 10a. Isolated in 63% yield after 19 h, mp 80–81 °C (from diethyl ether–hexane) (Found: C, 70.6; H, 7.0; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); ν_{max}(Nujol)/cm^{-1} 1746; δ_H(400 MHz) 2.31 (3 H, s), 2.49 (1 H, ddd, *J* 19.0, 5.4 and 2.3, H-5$_\beta$), 3.00 (1 H, dd, *J* 19.0 and 6.0, H-5$_\alpha$), 3.37 (1 H, s, H-7), 3.46 (3 H, s), 3.64 (3 H, s), 4.99 (1 H, bs, H-2), 5.58 (1 H, dm, *J* 10.6, H-3), 5.81 (1 H, ddt, *J* 10.6, 6.0 and 2.3, H-4), 7.08 (2 H, d, *J* 7.8) and 7.27 (2 H, d, *J* 7.8); δ_C(74.5 MHz) 21.09 (Ar-Me), 23.43 (C-5), 41.39 (C-7), 47.86 (C-6), 51.81 (OMe), 56.66 (OMe), 85.36 (C-2), 123.59 (C-3), 124.34 (C-4), 127.38, 128.64, 132.96, 136.79 and 170.00; *m*/*z* 273 (M^+).

Methyl 7-(2,6-dichlorophenyl)-2-methoxy-1-azabicyclo[4.1.0]-hept-3-ene-6-carboxylate 10b. Isolated in 60% yield after 24 h, mp 90–91 °C (from diethyl ether–hexane) (Found: C, 55.0; H, 4.6; N, 4.2. $C_{15}H_{15}Cl_2NO_3$ requires C, 54.9; H, 4.6; N, 4.3%); ν_{max}(Nujol)/cm^{-1} 1711; δ_H(400 MHz) 2.70 (1 H, ddd, *J* 18.7, 5.6 and 2.3, H-5$_\beta$), 3.06 (1 H, dd, *J* 18.7 and 6.4, H-5$_\alpha$), 3.44 (3 H, s), 3.58 (1 H, s, H-7), 3.78 (3 H, s), 4.95 (1 H, bs, H-2), 5.57 (1 H, dm, *J* 9.0, H-3), 5.92 (1 H, ddt, *J* 9.0, 6.4 and 2.3, H-4), 7.08 (1 H, d, *J* 8.0) and 7.25 (2 H, d, *J* 8.0); δ_C(74.5 MHz) 23.05 (C-5), 40.65 (C-7), 44.37 (C-6), 52.11 (OMe), 58.65 (OMe), 86.27 (C-2), 124.33 (C-3), 125.96 (C-4), 128.07, 128.38, 131.83, 135.89 and 170.74; *m*/*z* 327, 329 and 331 (M^+).

Methyl 2-methyl-7-(4-methylphenyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 11a. Isolated in 46% yield after 72 h as an oil (Found: C, 74.3; H, 7.6; N, 5.6. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.4; N, 5.4%); ν_{max}(film)/cm^{-1} 1750 and 1720; δ_H(300 MHz) 1.26 (3 H, d, *J* 6.9, 2-Me), 2.30 (3 H, s), 2.53 (1 H, ddd, *J* 18.6, 5.1 and 2.3, H-5$_\beta$), 2.96 (1 H, dd, *J* 18.6 and 6.0, H-5$_\alpha$), 3.26 (1 H, s, H-7), 3.42 (3 H, s), 3.92–4.04 (1 H, m, H-2), 5.49 (1 H, dm, *J* 10.5, H-3), 5.73 (1 H, ddt, *J* 10.5, 6.3 and 2.4, H-4), 7.07 (2 H, d, *J* 7.5) and 7.25 (2 H, d, *J* 7.5); δ_C(74.5 MHz), 20.34 (2-Me), 20.99 (Ar-Me), 22.75 (C-5), 40.75 (C-7), 47.65 (C-6), 49.97 (C-2), 51.65 (OMe), 121.50 (C-3), 126.93 (C-4), 127.51, 128.65, 133.65, 136.76 and 171.00; *m*/*z* 257 (M^+).

Methyl 7-(2,5-dichlorophenyl)-2-methyl-1-azabicyclo[4.1.0]-hept-3-ene-6-carboxylate 11b. Isolated in 78% yield after 5 days, mp 40.5–41.5 °C (from diethyl ether–hexane) (Found: C, 57.7; H, 4.8; N, 4.5. $C_{15}H_{15}Cl_2NO_2$ requires C, 57.7; H, 4.8; N, 4.5%); ν_{max}(Nujol)/cm^{-1} 1713; δ_H(300 MHz) 1.49 (3 H, d, *J* 7.8, 2-Me), 2.74 (1 H, ddd, *J* 18.8, 5.4 and 3.0, H-5$_\beta$), 3.07 (1 H, dd, *J* 18.8 and 6.5, H-5$_\alpha$), 3.37 (3 H, s), 3.46 (1 H, s, H-7), 4.01–4.07 (1 H, m, H-2), 5.34 (1 H, bd, *J* 10.2, H-3), 5.80–5.87 (1 H, m, H-4), 7.07 (1 H, d, *J* 8.1) and 7.25 (2 H, d, *J* 8.1); δ_C(74.5 MHz) 20.87 (2-Me), 22.50 (C-5), 40.52 (C-7), 45.99 (C-6), 51.70 (C-2), 51.97 (OMe), 122.94 (C-3), 126.68 (C-4), 128.07, 128.55, 132.19, 135.83 and 171.20; *m*/*z* 311, 313 and 315 (M^+).

Methyl 7-(4-methylphenyl)-4-trimethylsilyloxy-1-azabicyclo-[4.1.0]hept-3-ene-6-carboxylate 12. Isolated in 42% yield after 48 h as an oil (Found: M^+, 331.160. $C_{18}H_{25}NO_3Si$ requires *M*, 331.160); ν_{max}(Nujol)/cm^{-1} 1753, 1723 and 1676; δ_H(300 MHz) 0.55 (9 H, s), 2.30 (3 H, s), 2.57 (1 H, dd, *J* 18.0 and 1.8, H-5$_\beta$), 2.94 (1 H, d, *J* 18.0, H-5$_\alpha$), 3.32 (1 H, s, H-7), 3.43 (3 H, s), 3.64 (1 H, dd, *J* 17.4 and 5.4, H-2$_\beta$), 4.02 (1 H, d, *J* 17.4, H-2$_\alpha$), 4.66–4.68 (1 H, m, H-3), 7.08 (2 H, d, *J* 7.9) and 7.23 (2 H, d, *J* 7.9); δ_C(75.5 MHz) 0.23 ($SiMe_3$), 20.68 (Ar-Me), 28.17 (C-5), 43.41 (C-7), 46.93 (C-2), 48.62 (C-6), 51.5 (OMe), 97.14 (C-3), 127.20, 128.46, 132.63, 136.64, 145.49 (C-4) and 170.40.

Methyl 4-methyl-7-(4-methylphenyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 13 and methyl 3-methyl-7-(4-methylphenyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 14. Isolated as an oily mixture in 69% yield after 72 h; characterised only by ^{1}H NMR spectroscopy; δ_H(200 MHz) 1.64 (3-Me of **14**), 1.76 (4-Me of **13**), 5.27 (H-3 of **13**) and 5.46 (H-4 of **14**); other signals were not assigned. The ratio of **13**:**14**, estimated from the H-3 and H-4 signal intensities, was 2.7:1.

Methyl 2-methoxy-7-(4-methylphenyl)-4-trimethylsilyloxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 15a and methyl 2-methoxy-7-(4-methylphenyl)-4-oxo-1-azabicyclo[4.1.0]heptane-6-carboxylate 16a. After reaction for 15 min and purification by flash chromatography the silyl ether **15a** (25%) was isolated as an oil (Found: M^+, 361.171. $C_{19}H_{27}NO_4Si$ requires *M*, 361.170); ν_{max}(film)/cm^{-1} 1723 and 1665; δ_H(300 MHz) 0.24 (9 H, s), 2.30 (3 H, s), 2.51 (1 H, d, *J* 18.3, H-5$_\beta$), 2.92 (1 H, d, *J* 18.3, H-5$_\alpha$), 3.32 (1 H, s, H-7), 3.45 (3 H, s), 3.62 (3 H, s), 4.67 (1 H, s, H-3), 5.16 (1 H, s, H-2), 7.08 (2 H, d, *J* 8.1) and 7.28 (2 H, d, *J* 8.1). Further elution gave the ketone **16a** (24%), mp 99.5–100 °C (from diethyl ether–hexane) (Found: C, 66.4; H, 6.6; N, 4.8. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8%); ν_{max}(Nujol)/cm^{-1}

‡ The numbering system for the NMR assignments follows that shown on the structure of **6**.

1746 and 1714; δ_H(400 MHz) 2.30 (3 H, s), 2.49 (1 H, dd, *J* 17.9 and 5.3, H-3), 2.70 (1 H, dd, *J* 17.9 and 3.5, H-3′), 2.93 (1 H, d, *J* 18.4, H-5), 3.08 (1 H, d, *J* 18.4, H-5′), 3.43 (3 H, s), 3.48 (1 H, s, H-7), 3.49 (3 H, s), 5.09 (1 H, dd, *J* 5.3 and 3.5, H-2), 7.10 (2 H, d, *J* 8.1) and 7.31 (2 H, d, *J* 8.1); δ_C(74.5 MHz) 21.13 (Ar-Me), 39.32, 42.58 (C-3, C-5), 46.80 (C-6), 47.25 (C-7), 52.17 (OMe), 57.36 (OMe), 87.38 (C-2), 127.26, 128.56, 131.77, 137.61, 165.21 and 204.22; *m*/*z* 289 (M^+).

Methyl 7-(2,6-dichlorophenyl)-2-methoxy-4-trimethylsilyloxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 15b and methyl 7-(2,6-dichlorophenyl)-2-methoxy-4-oxo-1-azabicyclo[4.1.0]heptane-6-carboxylate 16b. After reaction for 48 h and purification by flash chromatography the silyl ether **15b** (61%) was isolated as an oil. The compound was not obtained completely pure and was characterised only by ^{1}H NMR spectroscopy; δ_H(200 MHz) 0.25 (9 H, s), 2.78 (1 H, d, *J* 17.9, H-5$_\beta$), 2.97 (1 H, d, *J* 17.9, H-5$_\alpha$), 3.43 (3 H, s), 3.56 (1 H, s, H-7), 3.75 (3 H, s), 4.64 (1 H, s, H-3), 5.09 (1 H, s, H-2), 7.12 (1 H, t, *J* 7.8) and 7.27 (2 H, d, *J* 7.8). Further elution gave the ketone **16b** (17%), mp 108–110 °C (from diethyl ether–hexane) (Found: C, 52.4; H, 4.4; N, 4.1. $C_{15}H_{15}Cl_2NO_4$ requires C, 52.4; H, 4.4; N, 4.1%); ν_{max}(Nujol)/cm^{-1} 1726; δ_H(400 MHz) 2.63–2.67 (2 H, m, H-3 and H-3′), 2.66 (1 H, d, *J* 18.2, H-5), 3.45 (3 H, s), 3.54 (3 H, s), 3.59 (1 H, d, *J* 18.2, H-5′), 3.62 (1 H, s, H-7), 5.25 (1 H, t, *J* 2.9, H-2), 7.18 (1 H, t, *J* 8.4) and 7.32 (2 H, d, *J* 8.4); δ_C(74.5 MHz) 38.20, 43.65 (C-3, C-5), 44.11 (C-6), 47.79 (C-7), 52.68 (OMe), 58.12 (OMe), 87.18 (C-2), 128.33, 128.98, 131.77, 135.49, 169.81 and 201.22; *m*/*z* 343, 345 and 347 (M^+).

Reaction of the ether 7 with water. Methyl 7-(2,6-dichlorophenyl)-2,5-dihydroxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate 8. A drop of water was added to a neat sample of the ether **7**. It was rapidly converted into an oil that, after drying, gave a foam (Found: C, 51.1; H, 3.9; N, 4.2. $C_{14}H_{13}Cl_2NO_4$ requires C, 50.9; H, 4.0; N, 4.2%); ν_{max}(film)/cm^{-1} 3297 and 1728; δ_H(400 MHz) 3.63 (3 H, s), 3.65 (1 H, s, H-7), 5.62 (1 H, t, *J* 1.6, H-5), 5.85 (1 H, bs, H-2), 6.04 (1 H, ddd, *J* 6.0, 1.6 and 1.2, H-3), 6.09 (1 H, ddd, *J* 6.0, 1.6 and 0.6, H-4), 7.17 (1 H, t, *J* 7.8) and 7.29 (2 H, d, *J* 7.8); δ_C(74.5 MHz) 42.90 (C-6), 45.91 (C-7), 52.89 (OMe), 80.17 (C-5), 102.68 (C-2), 128.51, 129.24, 129.35, 131.19, 131.64, 135.61 and 169.80; *m*/*z* (CI) 330 [$(M + H)^+$].

Crystal data for 9

$C_{17}H_{19}NO_4$, $M = 301.33$. Triclinic, $a = 9.678(8)$, $b = 12.910(6)$, $c = 6.617(7)$ Å, $\alpha = 95.48(7)°$, $\beta = 104.257(8)°$, $\gamma = 97.84(5)°$, $V = 786.7(11)$ Å^3, $F(000)$ 320, $\lambda = 0.710\,73$ Å, $T = 153(2)$ K, space group $P\bar{1}$, $Z = 2$, $D_c = 1.272$ g cm^{-3}, clear prism, 0.40 × 0.15 × 0.05 mm.

Data collection and processing

Rigaku AF6S diffractometer, graphite-monochromated Mo-Kα radiation, ω–2θ scans to a maximum 2θ value of 50.0° with ω scan width $(1.1 + 0.30 \tan \theta)°$; 2250 reflections collected of which 1788 were unique ($R_{int} = 0.0386$). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection; no decay correction was applied. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.72 to 1.00.

Structure solution and refinement

Automatic direct methods[14] (all non-H atoms). Non-H atoms were refined either anisotropically or isotropically. The final cycle of full-matrix least-squares refinement was based on 1788 observed reflections [$I > 2.00\sigma(I)$] and 236 variable parameters and converged (largest parameter shift was 0.06 times its esd) with weighted and unweighted agreement factors of:

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0843$$

$$R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2)]^{\frac{1}{2}} = 0.2021$$

The standard deviation of an observation of unit weight was 7.73. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.414 and −0.358 e Å^{-3}, respectively. All calculations were performed using the TEXSAN crystallographic structure package of the Molecular Structure Corporation.[15]

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/171.

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