Hydroxylation of 1-azabicyclo[4.1.0]hept-3-enes formed by Diels–Alder reactions of benzyl 2*H*-azirine-3-carboxylate

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Dedicated to Professor Charles Rees, CBE, FRS, on his 75th birthday

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Abstract

Benzyl 2*H*-azirine-3-carboxylate **1b** added as a dienophile to several cyclic and acyclic conjugated dienes at room temperature to give derivatives of the 1-azabicyclo[4.1.0]hept-3-ene ring system. The cycloaddition reactions gave exclusively the products of *endo* addition with respect to the three membered ring, as shown by crystal structures of two of the compounds, **4c** and **4d**. Methods for the *cis*-hydroxylation of the double bonds of some of these compounds were explored and four dihydroxy compounds were isolated from the adducts with cyclohexa-1,3-diene, 1-acetoxybutadiene, 1,4-diacetoxybutadiene and 1,4-bis(*tert*-butyldimethylsilyloxy)butadiene, in each case as single isomers. The structure of one of these, compound **6**, was supported by an X-ray crystal structure determination. Methods for reduction of the benzyloxycarbonyl group to a hydroxymethyl group were also investigated with the aim of forming novel glycosidase inhibitors analogous to nojirimycin.

Keywords: Azirine, Diels–Alder reaction, hydroxylation

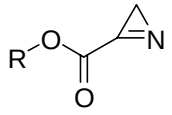
Introduction

In several publications we have described the reactions of 2*H*-azirines bearing an activating alkoxycarbonyl or aminocarbonyl substituent on the C=N bond with conjugated dienes.[1,2] The azirines proved to be highly active dienophiles, and Diels–Alder cycloaddition reactions took place at room temperature without a catalyst. Recently, similar reactions have been reported with 2*H*-azirines bearing an activating dialkoxyphosphonyl substituent.[3] In an attempt to simplify the azirine structure as much as possible the azirine ester **1a**, unsubstituted at C-2, was generated from *tert*-butyl acrylate.[2] This azirine is a good dienophile but it is very unstable and cannot be fully characterized. As an alternative the benzyl ester **1b** was prepared and it proved to be

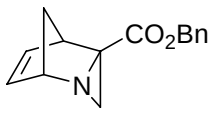
somewhat more stable and easier to handle. We have previously described the reactions of this azirine with some nitrogen heterocycles[4] and with furans.[5] Its reactions with other conjugated dienes have been investigated and are described here. The hydroxylation of the double bonds in the adducts obtained from the dienes, particularly those bearing oxygen substituents, have also been explored with the aim of finding a simple route to glycosidase inhibitors analogous to nojirimycin.

Results and Discussion

The azirine ester **1b** is generated by heating a toluene solution of benzyl 2-azidoacrylate under reflux for 5 h.[4] It can be isolated and characterized by NMR spectroscopy but for the purpose of carrying out cycloaddition reactions it is simpler to reduce the volume of the toluene solution under vacuum and to add the diene directly to the solution. In this way Diels–Alder reactions were performed at room temperature with cyclopentadiene, 1,3-cyclohexadiene, 1,4-diphenylbutadiene, 1-acetoxybutadiene, and 1,4-diacetoxybutadiene, giving the 1-azabicyclo[4.1.0]hept-3-enes **2**, **3** and **4a**–**4c** which were isolated and characterized. We have described the analogous synthesis of compound **4d** from 1,4-bis(*tert*-butyl-dimethylsilyl)butadiene earlier.[5]



1a; R = Bu^t
b; R = Bn



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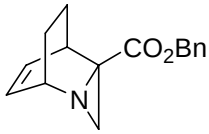

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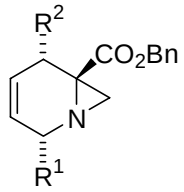


4a; $R^1 = R^2$ = Ph
b; R^1 = OAc, R^2 = H
c; $R^1 = R^2$ = OAc
d; $R^1 = R^2$ = $OSiMe_2Bu^t$

All these cycloaddition reactions were remarkably selective and gave only single isomers. The structures of two of these, compounds **4c** and **4d**, were established by X-ray crystallography (Figures 1 and 2). Selected bond lengths and bond angles are given in Tables 1 and 2. From these and from NMR data it is clear that the azirine approaches the diene in an *endo* manner with respect to the 3-membered ring.[1,2]

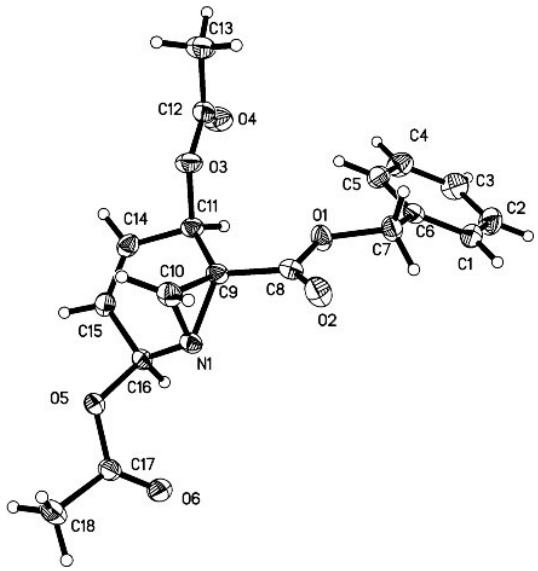


Figure 1. ORTEP view of the structure of the aziridine **4c**.

Table 1. Selected bond lengths and bond angles for **4c**[a]

Bond lengths (Å)		Bond angles (°)	
C9–N1	1.4800(13)	N1-C9-C10	59.33(7)
C9–C10	1.4890(14)	N1-C10-C9	60.03(7)
C10–N1	1.4694(14)	C10-N1-C9	60.64(7)
C9–C11	1.5127(14)	N1-C9-C11	120.57(9)
C16–N1	1.4684(14)	C14-C11-C9	113.24(9)
C11–C14	1.4941(16)	C15-C14-C11	122.26(10)
C14–C15	1.3222(16)	C14-C15-C16	121.94(10)
C15–C16	1.4982(14)	N1-C16-C15	116.10(9)
C16–O5	1.4437(12)	C16-N1-C9	116.85(8)
C11–O3	1.4614(13)	C10-C9-C11	118.04(9)
		C16-N1-C10	116.67(9)

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

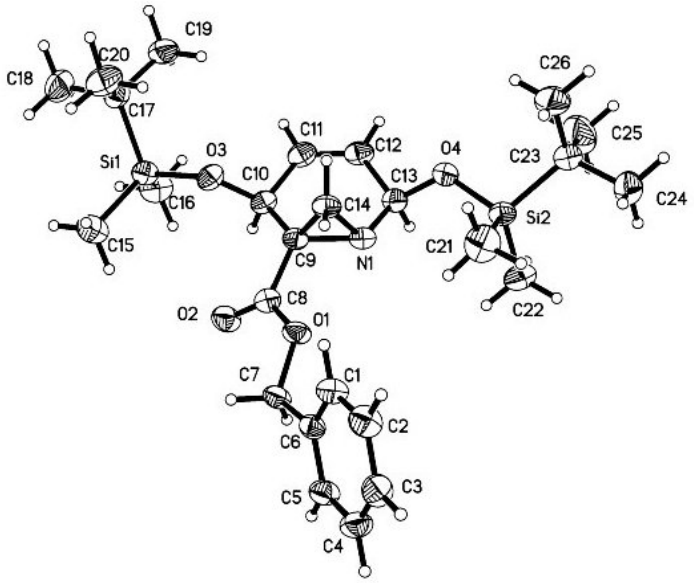


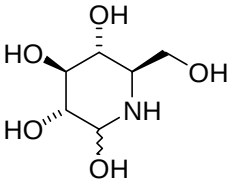
Figure 2. ORTEP view of the structure of the aziridine **4d**.

Table 2. Selected bond lengths and bond angles for **4d**[a]

Bond lengths (Å)		Bond angles (°)	
C9–N1	1.485(2)	C14–C9–N1	58.85(12)
C14–N1	1.458(2)	N1–C14–C9	60.62(12)
C9–C14	1.484(2)	C14–N1–C9	60.53(12)
C9–C10	1.520(2)	N1–C9–C10	121.31(16)
C10–C11	1.501(3)	C11–C10–C9	111.90(17)
C11–C12	1.309(3)	C12–C11–C10	124.13(18)
C12–C13	1.497(3)	C11–C12–C13	122.99(19)
C13–N1	1.470(2)	N1–C13–C12	115.48(17)
C13–O4	1.410(2)	C13–N1–C9	118.09(14)
C10–O3	1.425(2)	C14–N1–C13	116.46(15)
		C14–C9–C10	118.43(16)

[a] Atom numbering corresponds to that in Figure 2.

The chemistry of the 1-azabicyclo[4.1.0]hept-2-ene ring system has not previously been investigated and we were attracted by the potential for introducing further functional groups on the double bond. In particular, if those adducts containing oxygen substituents at positions 2 and 5 could be hydroxylated and the benzyloxycarbonyl group reduced, this would provide a very short route into glycosidase inhibitors similar in structure to nojirimycin **5**. Several inhibitors of this type that contain an aziridine ring have been described in the literature.[6] Some preliminary experiments were first carried out with the cyclohexadiene adduct **3** in order to check that the 3-membered ring would survive treatment with oxidising and reducing agents. Reduction with lithium aluminium hydride gave the alcohol **6** which was isolated in 49% yield after chromatography. The *cis*-hydroxylation of the double bond of the ester **3** was achieved by reaction with a catalytic amount of osmium tetroxide and with *N*-methylmorpholine *N*-oxide as co-oxidant; this gave the diol **7** in 42% yield.



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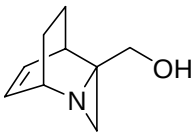

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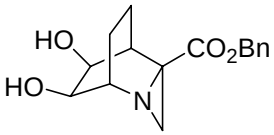

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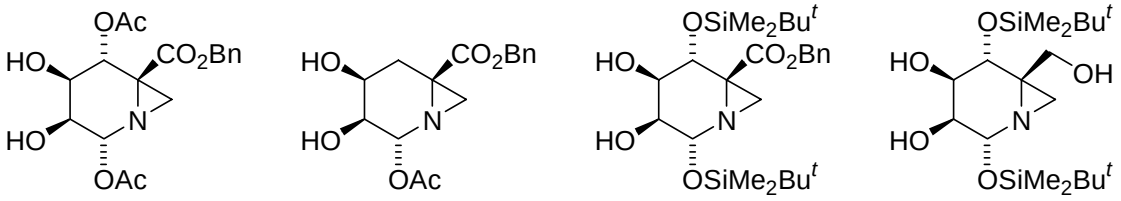
Having established that the 3-membered ring could survive these conditions, a similar hydroxylation was attempted with the diacetate **4c**. However the compound remained unchanged after exposure to the reagents for 7 days, and the use of a stoichiometric amount of osmium tetroxide caused it to decompose. As an alternative we turned to the use of a quaternary ammonium permanganate salt for *cis*-dihydroxylation.[7] Cetyltrimethylammonium permanganate was made by a slight modification of the literature procedure and was obtained as a violet powder, soluble in dichloromethane. Hydroxylation of the double bond of the diacetate **4c** was carried out using this salt in dichloromethane at room temperature and the diol **8** was isolated in yields of up to 50% as a crystalline solid. Its structure was confirmed by an X-ray determination (Figure 3 and Table 3). The same method, when applied to the monoacetate **4b**, gave the corresponding diol **9** only in low yield and with the bis(silyl ether) **4d** the diol **10** was isolated in, at best, 23% yield. However when this last hydroxylation was carried out under standard osmylation conditions with a catalytic amount of osmium tetroxide, the diol **10** was obtained in 93% yield. It may be that osmylation of the diacetate **4c** is inhibited by the two electron deficient oxygen substituents.



8 **9** **10** **11**

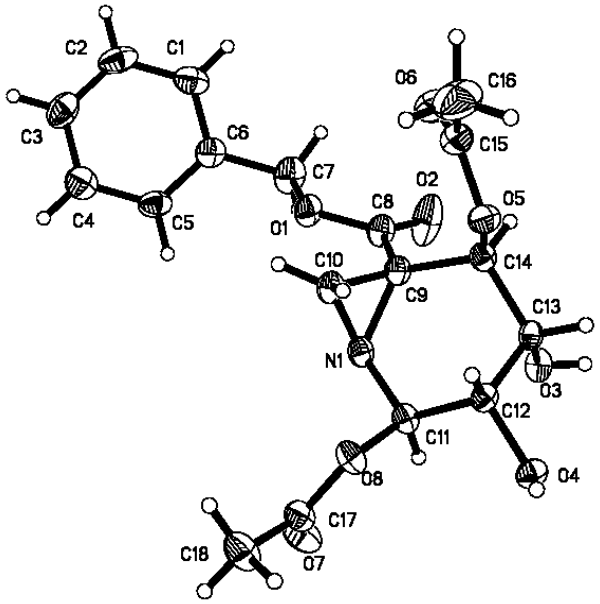


Figure 3. ORTEP view of the structure of the aziridine **8**.

Table 3. Selected bond lengths and bond angles for **8**[a]

Bond lengths (Å)		Bond angles (°)	
C9–C10	1.4810(19)	C10–C9–N1	59.31(8)
C9–N1	1.4970(17)	C10–N1–C9	59.80(9)
C10–N1	1.4735(17)	N1–C10–C9	60.89(9)
C11–N1	1.4745(17)	N1–C9–C14	119.91(10)
C11–C12	1.5212(17)	N1–C11–C12	117.62(11)
C12–C13	1.5133(18)	C13–C12–C11	109.49(10)
C13–C14	1.5172(18)	C12–C13–C14	109.54(10)
C9–C14	1.5249(18)	C13–C14–C9	112.65(11)
C14–O5	1.4441(16)	C11–N1–C9	118.50(10)
C11–O8	1.4315(16)	C10–C9–C14	119.80(11)
		C10–N1–C11	115.40(10)

[a] Atom numbering corresponds to that in Figure 3.

Finally a small scale reduction of the benzyloxycarbonyl group of the diol **10** was carried out. This gave the triol **11** (31%) as an oil. The final deprotection of the silyl ether functions was not attempted but overall this appears to be a viable route to polyhydroxylated 1-azabicyclo[4.1.0]heptanes, albeit in racemic form. Epoxidation of the double bond of the precursor **4d** and further functional group manipulation could enable diastereoisomers to be synthesized.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz), on a Varian Gemini 2000 (300 MHz) or on a Varian Avance 400 (400 MHz) instrument. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t) and multiplets (m). *J* Values are in Hz. ^{13}C spectra were recorded on the Varian Gemini instrument at 75.5 MHz or on the Avance 400 instrument at 100.6 MHz. All spectra were recorded using tetramethylsilane (TMS) as the internal reference. IR spectra were recorded in the range of 4000 to 600 cm^{-1} using either a Perkin-Elmer 883 or a Perkin Elmer Paragon 1000 machine. Solid samples were run as KBr discs, and liquids as thin films. Mass spectra were recorded on a VG Analytical 7070E or a Trio 1000 Quadrupole GC mass spectrometer, either under electron impact (EI) or chemical ionization (CI). Microanalyses were performed in the University of Liverpool Department of Chemistry microanalytical laboratory using a Carlo Erba elemental analyser. Melting points were determined on a Kofler block and are uncorrected. Flash column chromatography was carried out using Kieselgel 60 and hand bellows or an air line to supply the pressure to the column. 1,3-Cyclohexadiene, 1,4-diphenylbutadiene, 1-acetoxybutadiene and 1,4-diacetoxybutadiene are commercially available and were used as supplied. Cyclopentadiene was obtained by pyrolysis of the dimer. 1,4-Bis(*tert*-butyldimethylsilyloxy)butadiene was prepared by a literature procedure.[8]

Benzyl 2,3-dibromopropionate. Bromine (4.8 g, 30.0 mmol) was added dropwise to a solution of benzyl acrylate (5.00 g, 30.1 mmol) in dichloromethane (70 ml) at 0 ^{o}C. The solvent was evaporated to yield benzyl 2,3-dibromopropionate (9.78 g, 98%) as a pale yellow oil (Found: C, 37.02; H, 3.08. $C_{10}H_{10}Br_2O_2$ requires C, 37.30; H, 3.13%); ν_{max} (film)/cm^{-1} 1744 (C=O), 1246, 1146, 974, 751 and 696; δ_H (300 MHz, $CDCl_3$) 3.68 (1 H, dd, *J* 9.9and 4.5 Hz, H-3), 3.95 (1 H, dd, *J* 11.1 and 9.9 Hz, H-2), 4.49 (1 H, dd, *J* 11.1 and 4.5 Hz, H-3), 5.26 (2 H, s, benzyl CH_2) and 7.38 (5 H, s, Ar); δ_C (75.5 MHz, $CDCl_3$) 29.6 (C-3), 41.1 (C-2), 68.2 (benzyl C), 128.4, 128.7, 128.9, 134.8 and 167.5 (C=O); *m/z* (EI) M^+ 324 (0.2)/322 (0.4)/320 (0.2), 241 (12), 169 (22), 107 (33) and 91(100).

Benzyl 2-azidoacrylate. To a solution of sodium azide (1.22 g, 18.76 mmol) in DMF (45 ml) at 65 ^{o}C was added benzyl 2,3-dibromopropionate (2.0 g, 6.21 mmol). After 8 min. the reaction mixture was poured into water (100 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with water (3 x 50 ml), dried over $MgSO_4$, filtered and evaporated in vacuo to afford benzyl 2-azidoacrylate as a yellow oil (1.20 g, 95%) (Found: *C,* 59.33; H, 4.47; N, 20.88. $C_{10}H_9N_3O_2$ requires C, 59.11; H, 4.46; N, 20.68%); ν_{max} (film)/cm^{-1} 2113 (azide) and 1724 (C=O); δ_H (300 MHz, $CDCl_3$) 5.26 (2 H, s, benzyl CH_2), 5.34 (1 H, d, *J* 1.9 Hz, H-3), 5.85 (1 H, d, *J* 1.9 Hz, H-3) and 7.37 (5 H, s); δ_C (75.5 MHz, $CDCl_3$) 67.7 (benzyl C), 111.2 (C-3), 128.4, 128.6, 128.7, 135.0, 136.2 (C-2) and 161.9 (C=O); *m/z* (CI, + NH_3) $[M + NH_4]^+$ 221 (100).

Benzyl 2-azatricyclo[3.2.1.0^{2,4}]oct-6-ene-4-carboxylate (2). Benzyl 2-azidoacrylate (0.39 g, 1.92 mmol) was heated under reflux in in toluene (100 ml) for 5 h. The solution was reduced in volume to *ca*. 20 ml and freshly distilled cyclopentadiene (1.98 g, 30 mmol) was added. After 10 h at RT the ester **2** (1.16 g, 60%) was isolated by flash chromatography (toluene–ether (10:3). (Found: HRMS (EI) M^+ 241.11019. $C_{15}H_{15}NO_2$ requires 241.11019); ν_{max} (film)/cm^{-1} 1724 (C=O), 1455, 1339, 1237, 1091, 748 and 697; δ_H (400 MHz, $CDCl_3$) 1.69 (1 H, s, H-3), 1.80 (1 H, dd, *J* 8.0 and 2.9 Hz, H-8), 2.18 (1 H, dt, *J* 8.0 and 1.8 Hz, H-8), 2.49 (1 H, d, *J* 3.0 Hz, H-3), 3.52 (1 H, t, *J* 1.4 Hz, H-5*),* 4.12 (1 H, br s, H-1), 5.12 (1 H, d, *J* 12.4 Hz, benzyl CH), *5.29* (1 H, d, *J* 12.4 Hz, benzyl CH), 5.65 (1 H, dd, *J* 5.3 and 2.0 Hz, H-7), 6.16 (1 H, m, H-6) and 7.35-7.31 (5 H, m); δ_C (100.6 MHz, $CDCl_3$) 43.4 (C-3), 43.7 (C-4), 44.9 (C-5), 61.2 (C-8), 66.8 (C-1), 67.3 (benzyl C), 128.4 (C-7), 128.45, 128.5, 128.6, 128.9, 133.5 (C-6), 136.3 and 173.3 (C=O).

The aziridine esters **3** and **4** (**a–c**) were prepared in the same way as compound **2** and were isolated and characterized as described below. The analogous preparation of the ester **4d** has been described earlier.[5]

Benzyl 2-azatricyclo[3.2.2.0^{2,4}]non-6-ene-4-carboxylate (3). From benzyl 2-azidoacrylate (1.00 g, 6.0 mmol) and cyclohexa-1,3-diene (1.00 g, 12.5 mmol); isolated as an oil (0.51 g, 60%) after 12 h by flash chromatography [hexane–ethyl acetate (1:1)]. (Found: HRMS (CI, + NH_3): $[M+1]^+$ 256.13389. $C_{16}H_{18}NO_2$ requires 256.13375); ν_{max} (film)/cm^{-1} 1721 (C=O), 1455, 1279, 1140, 1091, 897 and 697; δ_H (400 MHz, $CDCl_3$) 1.13–1.16 (1 H, m, H-9), 1.31–1.37 (1 H, m, H-8), 1.43 (1 H, s, H-3), 1.69 (1 H, s, H-3), 1.69–1.74 (1 H, m, H-9), 1.93–1.97 (1 H, m, H-8), 3.26–3.30 (1 H, m, H-5*),* 3.87-3.90 (1 H, m, H-1), 5.08 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.29 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.64 (1 H, m, H-7), 6.16 (1 H, m, H-6) and 7.25-7.35 (5 H, m); δ_C (100.6 MHz, $CDCl_3$) 20.9 (C-9), 24.5
(C-8), 29.1 (C-5), 29.8 (C-3), 39.4 (C-4), 52.8 (C-1), 67.1 (benzyl C), 125.9 (C-7), 128.1, 128.2, 128.5, 131.1 (C-6), 136.3 and 172.7 (C=O).

Benzyl 2,5-diphenyl-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (4a). From benzyl 2-azidoacrylate (0.20 g, 0.98 mmol) and 1,4-diphenyl-1,3-butadiene (0.23 g, 1.11 mmol); isolated as a yellow oil (0.09 g, 24%) after 7 days by chromatography on silica gel [hexane–ethyl acetate (4:1)]. (Found: HRMS (CI, + NH_3) $[M+1]^+$ 382.18048. $C_{26}H_{24}NO_2$ requires 382.18073); ν_{max}

(film)/cm^{-1} 1735 (C=O), 1236, 1170, 753, 736 and 697; δ_H (400 MHz, $CDCl_3$) 2.27 (1 H, s, H-7), 2.35 (1 H, s, H-7), 4.37 (1 H, br d, *J* 2.8 Hz, H-5), 4.88 (1 H, br d, *J* 2.0 Hz, H-2), 5.07 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.13 (1 H, d, *J* 12.6 Hz, benzyl CH), 5.80 (1 H, dt, *J* 10.4 and 2.5 Hz, H-3), 5.89 (1 H, dt, *J* 10.4 and 2.5 Hz, H-4) and 7.17-7.47 (15 H, m); δ_C (100.6 MHz, $CDCl_3$) 27.9 (C-7), 37.9 (C-5), 45.7 (C-6) 58.5 (C-2), 67.3 (benzyl C), 125.1 (C-3),127.4, 127.9, 128.3, 128.4, 128.8, 128.9, 129.0, 129.4 (C-3), 141.7, 142.6 and 170.2 (C=O).

Benzyl 2-acetoxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (4b). From benzyl-2-azidoacrylate (0.25 g, 1.24 mmol) and 1-acetoxybutadiene (0.4 ml, 2.06 mmol); isolated as an oil (0.10 g, 28%) after 3 days by chromatography on silica gel [hexane–ethyl acetate (1:1)]. (Found: HRMS (CI, + NH_3) $[M+1]^+$ 288.12284. $C_{16}H_{18}NO_4$ requires 288.12360); ν_{max} (film)/cm^{-1} 1737 (C=O), 1288, 1166, 743 and 696; δ_H (400 MHz, $CDCl_3$) 2.12 (3 H, s), 2.22 (1 H, s, H-7), 2.26 (1 H, s, H-7), 2.68 (1 H, dd, *J* 18.8 and 6.2 Hz, H-5), 2.79 (1 H, dd, *J* 18.8 and 2.1 Hz, H-5), 5.11 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.28 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.42 (1 H, dt, *J* 10.6 and 1.5 Hz, H-3), 5.80–5.86 (1 H, m, H-4), 6.23 (1 H, br s, H-2) and 7.35 (5 H, s); δ_C (100.6 MHz, $CDCl_3$) 21.5 (CH_3), 22.2 (C-5), 30.3 (C-7), 38.4 (C-6), 67.5 (benzyl C), 79.9 (C-2), 122.4 (C-3), 125.4 (C-4), 128.6, 128.7, 128.9, 136.0, 169.9 (C=O) and 170.2 (C=O).

Benzyl 2,5-diacetoxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (4c). From benzyl-2-azidoacrylate (0.38 g, 1.89 mmol) and 1,4-diacetoxybutadiene (0.40 g, 2.37 mmol); isolated as a colourless crystalline solid m.p 97–98 ^oC (0.33 g, 55%) after 7 days by chromatography on silica gel [hexane–ethyl acetate (1:4)]. (Found: C, 62.60; H, 5.54; N, 4.05. $C_{18}H_{19}NO_6$ requires C, 62.60; H, 5.55; N, 4.06%); ν_{max} (KBr)/cm^{-1} 1748 (C=O), 1723 (C=O), 1286, 1188, 761 and 702; δ_H (400 MHz, $CDCl_3$) 1.97 (3 H, s) 2.13 (3 H, s), 2.32 (1 H, s, H-7), 2.45 (1 H, s, H-7), 5.18 (1 H, d, *J* 12.0 Hz, benzyl CH), 5.24 (1 H, d, *J* 12.0 Hz, benzyl CH), 5.47 (1 H, d, *J* 10.6 Hz, H-3), 5.70 (1 H, dt, *J* 10.6 and 1.6 Hz, H-4), 6.12 (1 H, d, *J* 2.0 Hz, H-5), 6.24 (1 H, d, *J* 1.4 Hz, H-2) and 7.31–7.36 (5 H, m); δ_C (100.6 MHz, $CDCl_3$) 21.1 (CH_3), 21.3 (CH_3), 30.0 (C-7), 40.1 (C-6), 64.5 (C-5), 67.8 (benzyl C), 79.7 (C-2), 124.0 (C-3), 126.9 (C-4), 128.7, 128.8, 128.9, 135.7, 169.5 (C=O), 169.6 (C=O) and 170.2 (C=O); *m*/*z* (EI) 345 (M^+, 0.02) and 91 (100).

(2-Azatricyclo[3.2.2.0^{2,4}]non-6-en-4-yl]methanol (6). Lithium aluminium hydride (0.17 g, 34.5 mmol) was added to a solution of the ester **3** (0.38 g, 1.49 mmol) in THF (15 ml). When all the starting material was consumed (TLC) the reaction mixture was quenched with a saturated solution of ammonium chloride (5 ml). The mixture was extracted with ethyl acetate (3 x 20 ml) and the organic extracts were washed with sat. aq. $NaHCO_3$ (20 ml), brine (20 ml) then dried over $MgSO_4$ and evaporated in vacuo. The crude product was subjected to column chromatography [toluene-acetone (1:1)] to give the alcohol **6** (0.11 g, 49%) as a colourless oil. (Found: HRMS (CI, + NH_3): $[M+1]^+$ 152.10776. $C_9H_{14}NO$ requires 152.10754). ν_{max} (film)/cm^{-1} 3356 (OH), 2946, 1644, 1458, 1049, 734 and 702; δ_H (400 MHz, $CDCl_3$)1.06–1.12 (1 H, m, H-9), 1.25 (1 H, s, H-3), 1.26 (1 H, s, H-3), 1.31–1.40 (1 H, m, H-8), 1.77-1.90 (2 H, m, H-9 and H-8), 2.36 (1 H, br s, OH), 2.65–2.68 (1 H, m, H-5), 3.62 (1 H, d, *J* 11.1 Hz, C*H*OH), 3.69 (1 H, d, *J* 11.1 Hz, C*H*OH), 3.77–3.79 (1 H, br m, H-1), 5.63 (1 H, m, H-7) and 6.16 (1 H, m, H-6); δ_C

(100.6 MHz, $CDCl_3$) 19.8 (C-9), 24.9 (C-8), 25.2 (C-5), 31.2 (C-3), 38.3 (C-4), 51.9 (C-1), 62.4 (*C*H_2OH), 125.5 (C-7) and 131.3 (C-6).

Benzyl 6,7-dihydroxy-2-azatricyclo[3.2.2.0^{2,4}]nonane-4-carboxylate (7). To a solution of the ester **3** (0.14 g, 0.55 mmol) in water–acetone (1:8) (10 ml) at room temp. was added *N*-methylmorpholine *N*-oxide (0.13 g, 1.1 mmol) then osmium tetroxide (0.03 ml of a 0.98M solution in toluene). After 4 h the starting material could no longer be detected by TLC. The reaction mixture was quenched with saturated aq. Na_2SO_3 and extracted with ethyl acetate (2 x 50 ml). The solvent was evaporated in vacuo to give a residue that precipitated when redissolved in the column eluent [toluene-acetone (1:1)]. This colourless solid was identified as the diol **7**. A further fraction was obtained after chromatography to give the diol **7** (total 0.067 g, 42%), m.p. 140–141 ^{o}C (Found: C, 66.56; H, 6.66; N, 4.84. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); ν_{max} (film)/cm^{-1} 3414 (OH), 1730 (C=O), 1232, 1168, 1064 and 740; δ_H (400 MHz, $CDCl_3$)1.48–1.68 (2 H, m, H-9 and H-8), 1.86–1.95 (2 H, m, H-9 and H-8), 1.98 (2 H, s, H-3), 2.73 (1 H, d, *J* 2.3 Hz, H-5), 2.87 (1 H, br s, OH) (signal removed by D_2O), 2.96 (1 H, br s, OH) (signal removed by D_2O), 3.31 (1 H, d, *J* 2.6 Hz, H-1), 3.78 (2 H, br s, H-6 and H-7), 5.09 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.27 (1 H, d, *J* 12.4 Hz, benzyl CH) and 7.32–7.35 (5 H, m**);** δ_C (100.6 MHz, $CDCl_3$) 13.8 (C-9), 18.2 (C-8), 28.5 (C-3), 30.6 (C-5), 40.7 (C-6), 52.9 (C-1), 63.4 (C-6 or C-7), 64.5 (C-6 or C-7), 67.0 (benzyl C), 128.1, 128.3, 128.6, 135.7 and 171.6 (C=O); *m*/*z* (EI) 289 (M^+, 0.15) and 91(100).

Benzyl 2,5-diacetoxy-3,4-dihydroxy-1-azabicyclo[4.1.0]heptane-6-carboxylate (8). A solution of cetyltrimethylammonium permanganate[7] (0.15 g, 0.37 mmol) in dichloromethane (1.5 ml) was added dropwise to a stirred solution of the ester 4c (40 mg, 0.116 mmol) in dichloromethane (0.5 ml) at room temp. Stirring was continued for 12 h then the mixture was diluted with ethyl acetate (10 ml) and filtered through a pad of celite and anhydrous $MgSO_4$. The pad was washed with ethyl acetate to remove all organic materials. If necessary another filtration was performed in order to remove all the coloured by-products. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography [toluene-acetone (1:1)] to afford the diol 8 as a colourless solid (22 mg, 50%). (Found: HMRS (CI, + NH_3): $[M+1]^+$ 380.13490. $C_{18}H_{22}NO_8$ requires 380.13452). ν_{max} (KBr)/cm^{-1} 3341 (OH), 1748 (C=O), 1733 (C=O), 1258, 1228, 1175, 1108, 1043, 1022 and 757; δ_H (400 MHz, $CDCl_3$) 2.05 (3 H, s), 2.15 (3 H, s), 2.32 (1 H, s, H-7), 2.45 (1 H, s, H-7), 2.68 (1 H, br s, OH) (signal removed by addition of D_2O), 2.98 (1 H, br s, OH) (signal removed by addition of D_2O), 3.71 (1 H, br d, *J* 5.6 Hz, H-3), 3.84 (1 H, dd, *J* 4.8 and 1.9 Hz, H-4),5.16 (1 H, d, *J* 12.4 Hz, benzyl CH), 5.24 (1 H, d, *J* 12.4 Hz, benzyl CH), 6.02 (1 H, d, J 5.0 Hz, H-5), 6.11 (1 H, d, *J* 6.1 Hz, H-2) and 7.34 (5 H, s); δ_C (100.6 MHz, $CDCl_3$) 20.8 (CH_3), 21.0 (CH_3), 32.4 (C-7), 44.1 (C-6), 67.7 (benzyl C), 68.5 (C-3), 69.7 (C-4), 70.81 (C-5), 82.2 (C-2), 128.1, 128.3, 128.6, 135.4, 169.3 (C=O), 169.9 (C=O) and 170.8 (C=O).

Benzyl 2-acetoxy-3,4-dihydroxy-1-azabicyclo[4.1.0]heptane-6-carboxylate (9). A solution of cetyltrimethylammonium permanganate (0.1 g, 0.247 mmol) in dichloromethane (1.5 ml) was added dropwise to a stirred solution of the ester **4b** (62 mg, 0.216 mmol) in dichloromethane (1.5 ml) at room temperature. After 24 h the product was isolated from the reaction mixture as described for compound **8**. The diol **9** (6 mg, 9%) was isolated as a solid but was not fully characterized; δ_H (200 MHz, $CDCl_3$) 1.97 (1 H, s, H-7), 2.08 (1 H, dd, *J* 15.3 and 3.9 Hz, H-5), 2.16 (3 H, s), 2.43 (1 H, s, H-7), 3.00 (1 H, dd, *J* 15.3 and 3.9 Hz, H-5), 3.45 (1 H, dd, *J* 6.8 and 2.6 Hz, H-3), 4.00 (1H, dd, *J* 6.8 and 3.9 Hz, H-4), 5.09 (1 H, d, *J* 12.3 Hz, benzyl CH), 5.27 (1 H, d, *J* 12.3 Hz, benzyl CH), 6.10 (1 H, d, *J* 6.8 Hz, H-2) and 7.35 (5 H, s); *m*/*z* (CI, + NH_3) 321 (M^+, 1.1), 108 (72), 98 (100) and 91 (73).

Benzyl 2,5-bis(*tert*-butyldimethylsilyloxy)-3,4-dihydroxy-1-azabicyclo[4.1.0]heptane-6-carboxylate (10). To a solution of the ester **4d** (0.10 g, 0.204 mmol) in a 1:8 mixture of water–acetone at room temperature (10 ml) was added *N*-methylmorpholine *N*-oxide (0.06 g, 0.51 mmol), then a solution of OsO_4 in toluene (39 mM) (0.32 ml, 0.0124 mmol). The mixture was left at room temp. until the starting material could no longer be detected by TLC (24 h) and quenched with sat. aq. Na_2SO_3. After stirring for 15 min the mixture was extracted with ethyl acetate (2 x 50 ml), and the extracts washed with brine (2 x30 ml) and dried over Na_2SO_4. The solvent was evaporated in vacuo to give the diol **10** (0.10 g, 93 %) as a colourless oil. (Found: HMRS (CI, + NH_3): $[M+1]^+$ 524.28458. $C_{26}H_{46}NO_6Si_2$ requires 524.28637); ν_{max} (film)/cm^{-1} 3350 (OH), 1730 (C=O), 1252, 1112, 1064, 870, 838 and 779; δ_H (400 MHz, $CDCl_3$) –0.02 (3 H, s), 0.07 (3 H, s), 0.18 (3 H, s), 0.20 (3 H, s), 0.84 (9 H, s), 0.94 (9 H, s), 1.99 (1 H, br s, OH), 2.13 (1 H, s, H-7), 2.18 (1 H, br s, OH), 2.26 (1 H, s, H-7), 3.48 (1 H, d, *J* 6.8 Hz, H-3), 3.66 (1 H, s, H-4), 4.99 (1 H, d, *J* 7.1 Hz, H-2), 5.03 (1 H, d, *J* 4.0 Hz, H-5), 5.16 (2 H, s, benzyl CH_2) and 7.30–7.34 (5 H, m); δ_C (100.6 MHz, $CDC1_3$) –4.75, –4.70, –4.5, –3.9, 18.3, 18.5, 26.1, 26.2, 32.6 (C-7), 47.6 (C-6), 67.3 (benzyl C), 68.6 (C-5), 70.0 (C-3), 73.2 (C-4), 82.9 (C-2), 128.1, 128.2, 128.5, 128.8, 129.0, 136.1 and 171.7 (C=O).

2,5-Bis(*tert*-butyldimethylsilyloxy)-6-hydroxymethyl-1-azabicyclo[4.1.0]heptane-3,4-diol (11). Lithium aluminium hydride in THF (1 M) (1.2 ml, 1.2 mmol) was added to a solution of the diol **10** (0.1 g, 0.19 mmol) in THF (10 ml) at 0 ^oC and the mixture was stirred for 10 min. The mixture was allowed to warm to room temp. and stirred for 2 h until all the starting material was consumed (TLC). The reaction mixture was quenched by successive addition of water (0.01 ml), NaOH 15% (0.01 ml) and water (0.03 ml). The mixture was extracted with ethyl acetate (3 x 20 ml) and the organic extracts were washed with sat. aq. $NaHCO_3$ (20 ml) and brine (20 ml) then dried over $MgSO_4$ and evaporated in vacuo. The crude product was subjected to column chromatography [toluene-acetone (1:1)] to give the triol **11** (25 mg, 31%) as a colourless oil. (Found: HMRS (CI, + NH_3): $[M+1]^+$ 420.26081 $C_{19}H_{42}NO_5Si_2$ requires 420.26016); ν_{max} (film)/cm^{-1} 3391 (OH), 2927, 1462, 1252, 1108, 871, 837 and 777; δ_H (400 MHz, $CDCl_3$) 0.10 (3 H, s), 0.11 (3 H, s), 0.17 (3 H, s), 0.18 (3 H, s), 0.88 (9 H, s), 0.93 (9 H, s), 1.68 (1 H, s, H-7), 2.15 (1 H, s, H-7), 2.17 (1 H, br s, OH), 2.38 (1 H, br s, OH), 2.74 (1 H, br, OH), 3.38 (1 H, d, *J*

10.6 Hz, C*H*OH), 3.57 (1 H, br d, *J* 6.8 Hz, H-3), 3.70–3.73 (1 H, m, under signal at 3.71, H-4), 3.71 (1 H, d, *J* 10.6 Hz, C*H*OH), 4.14 (1H, d, *J* 4.3 Hz, H-5) and 4.90 (1 H, d, *J* 6.8 Hz, H-2); δ_C (100.6 MHz, $CDC1_3$) –4.4, –4.1, –3.5, 18.6, 18.7, 26.3, 26.4, 293 (C-7), 49.2 (C-6), 65.2 (*C*H_2OH), 71.0 (C-5), 71.2 (C-3), 73.6 (C-4) and 83.2 (C-2).

Crystal structure determination for compound (4c). *Crystal data.* $C_{18}H_{19}NO_4$, M = 345.34, Monoclinic, *a* = 9.9622(5), *b* = 7.5936(4), *c* = 22.9164(13) Å, β = 94.9380(10)°, *U* = 1727.17(16) Å^3, *T* = 150(2) K, space group P $2_{1/c}$, *Z* = 4, μ(Mo–K_α) = 0.100 mm^{-1}, 10370 reflections measured, 3956 unique (R_{int} = 0.0 157) which were used in all calculations. The final *wR*(F^2) was 1.047 (all data).

Crystal structure determination for compound (4d). *Crystal data*. $C_{26}H_{43}NO_4Si_2$, M = 489.79, Triclinic, *a* = 6.4897(7), *b* = 12.7810(15), *c*= 18.3960(19) Å, α = 79.493(3)°, β = 84.508(2)°, γ = 75.584(2)°, *U* = 1451.0(3) Å^3, *T* = 150(2) K, space group P–1, *Z* = 2, μ(Mo–K_α) = 0.151 mm^{-1}, 8951 reflections measured, 6293 unique (R_{int} = 0.0361) which were used in all calculations. The final *wR*(F^2) was 0.850 (all data).

Crystal structure determination for compound (8). *Crystal data*. $C_{18}H_{21}NO_8$, M = 379.36, Monoclinic, *a* = 13.6238(9), *b* = 11.0320(8), *c* = 12.4839(9) Å, β = 102.7430(10)°, *U* = 1830.1(2) Å^3, *T* = 273(2) K, space group $P2_{1/c}$, *Z* = 4, μ(Mo–K_α) = 0.109 mm^{-1}, 11325 reflections measured, 4205 unique (R_{int} = 0.0819) which were used in all calculations. The final *wR*(F^2) was 0.966 (all data).

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