Long-range Substituent Effects on the Regioselectivity of One-carbon Ring Expansion of Norbornan-7-ones

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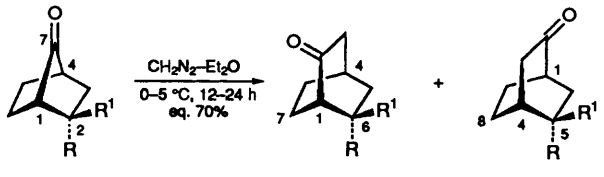
Ring-expansion regioselectivity in norbornan-7-ones can be substantially altered by the distal 2-substituents.

Diazomethane (DAM) is frequently employed for one-carbon ring expansion of mono- and poly-cyclic ketones, a valuable synthetic manoeuvre for gaining entry into higher homologues.[1] The regioselectivity in this transformation is not always predictable and exhibits marked dependence on the nature of the substrate and particularly on the substituents flanking the carbonyl group.[1c,e,f] Despite this limitation, DAM ring expansions have been extensively used for gaining access to a variety of bridged bi- and poly-cyclic systems.[1c] In connection with an ongoing project,[2,3] we required convenient access to several *endo*-substituted bicyclo[2.2.2]octanones and, since the latter are difficult to obtain by direct synthesis (*e.g.* Diels–Alder methodology), we considered preparing them through DAM-promoted ring expansion of the corresponding 2-*endo*-substituted norbornan-7-ones. However, the single literature report of 7-norbornanone ring expansion to give bicyclo[2.2.2]octan-2-one[4] does not involve any regiochemical issues. Herein, we report on the ring expansion of several *endo*-norbornan-7-ones to the corresponding bicyclo[2.2.2]octanones and disclose an interesting observation on the migratory preferences of the apparently equivalent C(1)–C(7) and C(4)–C(7) bonds in the ring expansion of norbornan-7-ones mediated by the distal C(2)-*endo*-substituent.

Results leading to the formation of ring-expanded bicyclo-[2.2.2]octanones **2a–d** and **3a–d** from **1a–d** are summarized in Scheme 1 and a typical procedure is detailed in the



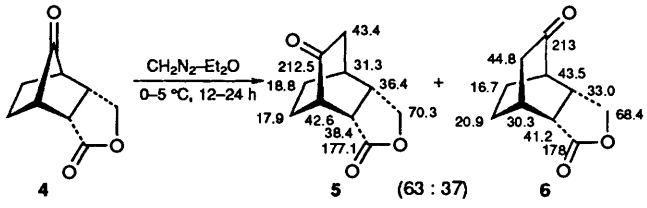
1 **2** **3**

a R = CO_2Me, R^1 = H
b R = CN, R^1 = H
c R = CH_2OMe, R^1 = H
d R = H, R^1 = CN

a (63 : 37)
b (71 : 29)
c (60 : 40)
d (61 : 39)

Scheme 1

Experimental section. Structures of regioisomeric ketones **2a–d** and **3a–d** are based on analyses of their ^{13}C NMR data (see Table 1). The major feature of the ^{13}C spectral assignment is that C-7 in the regioisomeric series **2a–c** is shielded both by the C-2 carbonyl as well as the C-6 *endo* substituent.[5,†] By comparison, in the **3a–c** series both C-7 and C-8 are shielded by the C-2 carbonyl and C-5 *endo* substituent, respectively. Thus, C(7)–C(8) ^{13}C resonances have larger separation in the **2a–c** series than in the **3a–c**. The shielding effect of the carbonyl is also discernible in the C-5 and C-6 resonances in both regioisomeric series. A similar analysis of the ^{13}C NMR shieldings in *exo*-**2d** and -**3d** led to their formulation (see Table 1). Like **1a–d**, the DAM ring expansion of the norbornan-7-one based *endo*-lactone **4** furnished synthetically useful bicyclo[2.2.2]octanones **5** and **6** with 63:37 regioselectivity, structural assignments for the latter follow from the ^{13}C NMR values depicted on their structures.



4 **5** (63 : 37) **6**

The results presented here indicate that the electron-withdrawing substituent (*e.g.*, CN, CO_2Me) at the C-2 *endo*-position significantly diminishes the propensity of the C(1)–C(7) bond to migrate *vs.* the C(4)–C(7) bond and **2b** is favoured over **3b** in the ratio 2.5:1. The lactone **4** also exhibits similar regioselectivity. Even the C-2 *exo*-cyano group in **1d** induces a similar migratory preference to furnish **2d** (61:39) and **3d**. Thus, the electronic effect of the C-2 substituent is operative in the ring expansion irrespective of its geometry. While the inductive effect of the α-substituents on the regioselectivity in DAM ring expansions is quite well precedented,[1c,e,f] this, to our knowledge, is the first example of a significant effect of the remote β-substituent on the regioselectivity of ring expansion. Admittedly, in an absolute sense, the regioselectivities observed here are quite modest but since such long-range inductive effects are uncommon they have potential in the synthesis of difficultly accessible regioisomers.[3]

Also, the above results have some bearing on the interpretation of the origin of face-selectivities in nucleophilic additions to *endo*-substituted norbornan-7-ones reported by us recently.[2] The predominant *syn*-selectivity observed for additions to norbornan-7-ones **1a–c** could be ascribed to concordant or discordant interplay between orbital and electrostatic effects. The orbital effects can be reconciled in terms of the Cieplak model[7] which emphasizes the importance of transition-state stabilization by hyperconjugation involving an electron donor bond and an adjacent incipient *anti*-bonding orbital (σ*).[2,3,6] This interpretation requires that the C(1)–C(2) bond in **1a–c** be electron deficient compared to the C(1)–C(6) bond as well as the C(3)–C(4) and C(4)–C(5) bonds. Our results indicate that this is indeed so, in the ground-state, as the C-2 substituent

† For comparison, ^{13}C NMR shifts for bicyclo[2.2.2]octane and bicyclo[2.2.2]octan-2-one are as follows:

Table 1

Substrate	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
2a	43.82	214.95	44.59	27.70	27.47	38.29	19.23	24.29
3a	41.82	216.01	44.47	31.47	41.17	25.35	22.47	20.64
2b	43.70	212.18	43.53	27.17	29.82	24.61	19.29	23.70
3b	41.06	213.19	43.53	31.41	26.70	27.94	22.35	20.58
2c	43.47	216.77	43.70	27.70	28.82	31.94	17.41	24.82
3c	42.35	217.59	45.41	28.94	35.35	27.29	23.23	19.11
2d	44.59	211.24	44.17	27.11	30.12	25.70	22.47	23.06
3d	40.88	213.12	40.88	31.53	26.17	27.82	22.00	24.06

^{13}C NMR spectra were recorded in $CDCl_3$. Assignments are based on internal consistency, off-resonance multiplicities in some cases and comparison with known bicyclo[2.2.2]octanones. Chemical shifts within 1–2 ppm range can be interchanged.

effect is felt even further in rendering the C(1)–C(7) bond electron deficient compared with the C(4)–C(7) bond which exhibits preferred migratory aptitude in the DAM ring expansion. Further efforts are currently being made to amplify these long-range effects to modulate stereo- and regio-selectivity in norbornan-7-one and related systems.

Experimental

DAM Ring Expansion of **1a**:[8] *General Procedure.*—To a solution of **1a** (430 mg, 2.56 mmol) in dry diethyl ether (6 cm^3) containing 10% methanol was added an excess of an ethereal solution of diazomethane at 0 °C until the yellow colour persisted. The reaction mixture was stored in the dark at 0–5 °C for 5 h during which time the reaction was monitored by TLC. Excess of DAM was destroyed with acetic acid when *ca.* 80% of **1a** had been consumed. Filtration through neutral alumina (hexane–ethyl acetate, 8:2) afforded a mixture of bicyclic ketones **2a** and **3a** (64%) in a ratio of 63:37 (GLC) which were separated by chromatography on silica gel and elution with hexane–ethyl acetate (9:1): **2a** m.p. 35–36 °C, ν_{max}(KBr)/cm^{-1} 2950, 1730 and 1200; δ_H(100 MHz, $CDCl_3$) 3.71 (3 H, s), 3.00–2.70 (1 H, m), 2.60 (1 H, m) and 2.36–1.50 (9 H, series of m) (Found: C, 65.85; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%); **3a** m.p. 64–65 °C, ν_{max}(KBr)/cm^{-1} 2950, 1730 and 1210; δ_H(100 MHz, $CDCl_3$) 3.72 (3 H, s) and 2.84–1.40 (11 H, series of m) (Found: C, 65.8; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

DAM Ring Expansion of **1b**.[8] The reaction, performed as described above, furnished **2b**:**3b** (71:29) in 68% yield; **2b**, m.p. 174–175 °C, ν_{max}(KBr)/cm^{-1} 2950, 2250, 1720 and 1110; δ_H(100 MHz, $CDCl_3$) 3.16–2.92 (1 H, m), 2.50 (1 H, m), 2.40–1.60 (9 H, series of m) (Found: C, 72.3; H, 7.45; N, 9.4. Calc. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39%); **3b** m.p. 167–168 °C; ν_{max}(KBr)/cm^{-1} 2950, 2250, 1720 and 1110; δ_H(100 MHz, $CDCl_3$) 2.96–2.72 (1 H, m) and 2.56–1.60 (10 H, series of m) (Found: C, 72.25; H, 7.4; N, 9.35. $C_9H_{11}NO$ requires C, 72.45; H, 7.43; N, 9.39%).

DAM Ring Expansion of **1c**. The reaction, performed as described above, furnished **2c**:**3c** (60:40) in 72% yield; **2c** ν_{max}(neat)/cm^{-1} 2950, 1720 and 1110; δ_H(100 MHz, $CDCl_3$) 3.30 (2 H, m), 3.24 (3 H, s), 2.30–1.40 (10 H, series of m) and 1.24–0.96 (1 H, m) (Found: C, 71.25; H, 9.55. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%); **3c** ν_{max}(neat)/cm^{-1} 2950, 1720 and 1110; δ_H(100 MHz, $CDCl_3$) 3.32–3.20 (5 H, m with a distinct s at 3.28) and 2.24–1.10 (11 H, series of m) (Found: C, 71.25; H, 9.55. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%).

DAM Ring Expansion of **1d**. The reaction, performed as described above, furnished **2d**:**3d** (61:39) in 66% yield; **2d**, m.p. 157–158 °C, ν_{max}(KBr)/cm^{-1} 2950, 2250, 1720 and 1100; δ_H(100 MHz, $CDCl_3$) 3.16–2.94 (1 H, m), 2.54 (1 H, m) and 2.44–1.60 (9 H, series of m) (Found: C, 72.4; H, 7.45; N, 9.3. $C_9H_{11}NO$ requires C, 72.45; H, 7.43; N, 9.39%); **3d** m.p. 147–148 °C, ν_{max}(KBr)/cm^{-1} 2950, 2250, 1720 and 1100; δ_H(100 MHz, $CDCl_3$) and 3.04–1.60 (11 H, series of m) (Found: C, 72.4; H, 7.45; N, 9.3. $C_9H_{11}NO$ requires C, 72.45; H, 7.43; N, 9.39%).

DAM Ring Expansion of **4**. The reaction, performed as described above, furnished **5**:**6** (63:37) in 55% yield; **5** m.p. 190–191 °C, ν_{max}(KBr)/cm^{-1} 2925, 1760, 1720 and 1170; δ_H(100 MHz, $CDCl_3$) 4.46 (1 H, dd, $J_1 = J_2$ 8), 4.20 (1 H, dd, J_1 10, J_2 4), 2.84 (2 H, m), 2.6 (1 H, m), 2.28 (1 H, br s), 2.16 (2 H, m), 1.80 (2 H, ½ABq, J 12) and 1.64 (2 H, ½ABq, J 12) (Found: C, 66.6; H, 6.8. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%); **6** m.p. 203–204 °C, ν_{max}(KBr)/cm^{-1} 2925, 1760, 1720 and 1170; δ_H(100 MHz, $CDCl_3$) 4.60–4.16 (2 H, m), 2.9 (2 H, m), 2.6 (1 H, m), 2.4–2.08 (3 H, m) and 2.00–1.60 (4 H, m) (Found: C, 66.6; H, 6.8. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%).

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