



one **1d** exhibits no regioselectivity and the lactones **2d** and **3d** are formed in near equal amounts. However, introduction of the electron-withdrawing substituent on the phenyl ring as in **1f–h** leads to preference for the formation of **2f–h** as compared to **3f–h**. On the other hand, the electron-donating methoxy group on the phenyl ring leads to a 'reversal' in regioselectivity with modest preference for the formation of **3e**. The absence of any migratory preference in the case of **1d** bearing an inductively electron-withdrawing phenyl group is quite unusual at first sight. We believe that the 2-*endo*-phenyl group acts as a through-bond  $\sigma$ -electron acceptor and a through-space  $\pi$ -donor into the C(1)–C(2)  $\sigma$ -bond of **1d**. Thus, the two effects are neutralized and the C(1)–C(2) bond is rendered equivalent to the C(3)–C(4) bond. Consequently, no regioselectivity is observed in the case of **1d**. However, in the case of the *o*-nitrophenyl **1g** and *p*-nitrophenyl **1h** derivatives, the  $\sigma$ -bond acceptor ability is amplified but the through-space  $\pi$ -donor capacity is diminished. This renders the C(1)–C(2) bond electron deficient and, in turn, reduces the migratory propensity of the C(1)–C(7) bond. Thus, regioisomers **2g,h** predominate over **3g,h**.

The norbornan-7-one derivatives, with the 2-*endo*-substituent located on the 'blind side' of the carbonyl group, are so constituted that steric and conformational effects have no bearing on the regioselectivity, which is a consequence of the through-bond electronic effects exerted by the substituent. These findings are fully concordant with our earlier interpretation<sup>5</sup> of the origin of face-selectivities in nucleophilic additions to *endo*-substituted norbornan-7-ones and more recent observations on regioselectivity during diazomethane ring-expansion.<sup>6</sup> The key element in these interpretations is the ability of the C(1)–C(2) bond to respond to the electron demand made by the C-2 substituent and transmit the same onto the stereo-induction centre at C-7 through the C(1)–C(7) bond.

In summary, the regioselectivities in the BV oxidation of norbornan-7-ones can be profoundly influenced by the 2-*endo*-substituent. In the case of 2-*endo*-substituted norbornan-7-one derivatives **1a–h**, steric and conformational effects are non-determinants of regioselectivity. In these compounds, the regioselectivities are wholly controlled by the electronic effects of the distal substituents. Our results indicate that long-range electronic control of BV oxidation regioselectivity is a much more general occurrence than has been recognized so far. In the case of the norbornan-7-ones **1a–g**, BV oxidation and hydrolysis provides a stereospecific route to a range of trisubstituted cyclohexanes.

## Experimental

### Baeyer–Villiger oxidation of **1d**: general procedure

To a solution of **1a** (17 mg, 0.0914 mmol) in  $\text{CH}_2\text{Cl}_2$  (5  $\text{cm}^3$ ) was added  $\text{NaHCO}_3$  (9 mg, 0.107 mmol) and *m*-CPBA (70%; 46 mg, 0.186 mmol) at 0–5 °C. After complete consumption of the starting material the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (20  $\text{cm}^3$ ) and then washed with 10% aqueous  $\text{Na}_2\text{SO}_3$ , saturated aqueous  $\text{NaHCO}_3$  and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. Filtration of the residue through a silica gel pad (hexane–ethyl acetate, 8:2) afforded a mixture of the bicyclic lactones **2d** and **3d** (18 mg, 97%) in a ratio of 51:49 (<sup>1</sup>H NMR and HPLC: Shimadzu Shimpack, HRC-SIL column, hexane–ethyl acetate, 8:2 eluent).

### Hydrolysis of the lactones **2d** and **3d**: general procedure

To a stirred solution of each of the above lactones (14 mg, 0.069 mmol) in MeOH– $\text{H}_2\text{O}$  (4:1; 4  $\text{cm}^3$ ) was added KOH (~6 mg, 0.1386 mmol). The resulting solution was stirred at room temp. for 3 h after which MeOH was removed under reduced pressure and the residue was acidified with 5% hydrochloric acid and extracted with ethyl acetate (3  $\times$  15  $\text{cm}^3$ ). The combined extracts were concentrated *in vacuo* and the residue was dissolved in ether–MeOH (9:1; 2  $\text{cm}^3$ ) to which an excess of

ethereal diazomethane was added at 0 °C until a yellow colour persisted. Excess of diazomethane was destroyed by the addition of acetic acid to the mixture which was then evaporated. The residue was chromatographed over silica gel (hexane–ethyl acetate, 8:2) to afford **4d** and **5d** (83%). *Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-phenylcyclohexanecarboxylate **4d**, mp 125–126 °C;  $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$  3279 (OH) and 1726 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.31–7.17 (5H, m, ArH), 4.24–4.22 (1H, m), 3.42 (3H, s), 3.38–3.22 (1H, m), 2.69–2.54 (1H, m), 2.13–1.56 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  175.27, 143.94, 128.40 (2C), 127.35 (2C), 126.49, 65.70, 51.26, 49.93, 40.26, 39.78, 31.61 and 23.83; *m/z* (EI) 234 ( $\text{M}^+$ , 11%), 216 ( $\text{M}^+ - 18, 15$ ) and 156 (100) (Found: 72.27; H, 7.54.  $\text{C}_{14}\text{H}_{18}\text{O}_3$  requires C, 71.77; H, 7.74%).

*Methyl* (4S\*,1R\*,3R\*)-4-hydroxy-3-phenylcyclohexanecarboxylate **5d**,  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3437 (OH) and 1730 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.35–7.25 (5H, m, ArH), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.68 (1H, dd, *J* 10, 4), 2.78–2.63 (2H, m), 2.37–2.30 (2H, m), 2.07–2.0 (1H, m) and 1.81–1.52 (3H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.80, 142.68, 128.69 (2C), 127.92 (2C), 126.84, 73.61, 51.67, 48.95, 39.12, 33.79, 31.09 and 26.01; *m/z* (EI) 216 ( $\text{M}^+ - 18, 14\%$ ), 156 (26), 104 (100) and 91 (38).

### Baeyer–Villiger oxidation of **1a** and hydrolysis to **4a**

The reaction performed as described above, furnished lactone **2a** in quantitative yield. The lactone was hydrolysed to give **4a** (>95%). *Methyl* (1S\*,2S\*,4R\*)-2-cyano-4-hydroxycyclohexanecarboxylate **4a**,  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3450 (OH), 2243 (nitrile) and 1736 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  4.15 (1H, m), 3.77 (3H, s), 3.33 (1H, td, *J* 9.8, 4.1), 2.64 (1H, td, *J* 9.6, 4.9), 2.14–1.49 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  172.59, 121.17, 64.21, 52.33, 44.74, 34.93, 31.24, 25.91 and 22.73; *m/z* (EI) 184 ( $\text{M}^+ + 1, 11\%$ ), 183 ( $\text{M}^+$ , 11), 154 (9), 138 (23), 124 (41), 80 (74) and 40 (100).

### Baeyer–Villiger oxidation of **1b** and hydrolysis to **4b**

The reaction performed as described above, furnished the lactones **2b:3b** (>90:10; 98.5%) which on hydrolysis gave **4b** (90%). *Dimethyl* (1S\*,2S\*,4R\*)-4-hydroxycyclohexane-1,2-dicarboxylate **4b**,  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3447 (OH) and 1736 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  4.13 (1H, br s), 3.67 (6H, s), 3.12 (1H, m), 2.66 (1H, m), 2.10–2.04 (1H, m) and 1.90–1.58 (5H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  175.53, 174.92, 64.85, 51.80 (2C), 44.14, 39.17, 35.08, 31.60, 30.14 and 22.60; *m/z* (EI) 216 ( $\text{M}^+$ , 1%), 184 ( $\text{M}^+ - 32, 38$ ), 138 (51), 97 (61) and 79 (100).

### Baeyer–Villiger oxidation of **1c** and hydrolysis to **4c** and **5c**

The reaction performed as described above, furnished the bicyclic lactones **2c:3c** (77:23; 86%) which upon hydrolysis yielded **4c** and **5c** (70%). *Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-methoxycyclohexanecarboxylate **4c**,  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3420 (OH) and 1736 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  4.2–4.1 (1H, m), 3.88–3.76 (1H, m), 3.69 (3H, s), 3.31 (3H, s), 2.42 (1H, td, *J* 9.4, 4) and 2.18–1.4 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.72, 76.19, 66.48, 56.59, 51.63, 48.20, 36.50, 31.66 and 22.55; *m/z* (EI) 188 ( $\text{M}^+$ , 12%), 173 (9), 155 (16), 110 (33) and 87 (100); (HRMS [ $\text{M}^+ - \text{CH}_3$ ], Found: 173.0820.  $\text{C}_8\text{H}_{13}\text{O}_4$  requires *M*, 173.0814).

*Methyl* (3S\*,4S\*,1R\*)-4-hydroxy-3-methoxycyclohexanecarboxylate **5c**,  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3435 (OH) and 1732 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  3.70 (3H, s), 3.6–3.5 (1H, m), 3.41 (3H, s), 3.29–3.18 (1H, m), 2.75 (1H, quintet, *J* 4), 2.40–2.28 (2H, m), 2.15–1.86 (2H, m) and 1.60–1.43 (2H, m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  175.04, 80.73, 71.43, 56.62, 51.63, 38.49, 28.56, 28.46 and 24.34; *m/z* (EI) 188 ( $\text{M}^+$ , 15%), 156 (60), 130 (88) and 111 (100).

### Baeyer–Villiger oxidation of **1e** and hydrolysis to **4e** and **5e**

The reaction performed as described above, furnished the bicyclic lactones **2e:3e** (39:61; quant. yield). The lactones were hydrolysed and chromatographed to give **4e** and **5e** (79%).

*Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-(4-methoxyphenyl)cyclohexanecarboxylate **4e**,  $\nu_{\max}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$  3431 (OH) and 1732 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.12 (2H, d, *J* 8.5), 6.82 (2H, d, *J* 8.7), 4.24 (1H, m), 3.77 (3H, s), 3.44 (3H, s), 3.24 (1H, td, *J* 11.8, 2.9), 2.59 (1H, td, *J* 11.7, 3.4) and 2.11–1.62 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  175.12, 158.24, 136.04, 128.25 (2C), 113.87 (2C), 65.92, 55.17, 51.17, 50.29, 40.48, 38.97, 31.68 and 23.84; *m/z* (EI) 264 ( $\text{M}^+$ , 33%), 246 ( $\text{M}^+ - \text{H}_2\text{O}$ , 44), 186 (100) and 121 (83).

*Methyl* (4S\*,1S\*,3R\*)-4-hydroxy-3-(4-methoxyphenyl)cyclohexanecarboxylate **5e**,  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3445 (OH) and 1730 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.19 (2H, d, *J* 8.1), 6.89 (2H, d, *J* 7.9), 3.80 (3H, s), 3.74 (3H, s), 3.70–3.59 (1H, m), 2.76 (1H, br s), 2.62 (1H, m), 2.34–2.25 (2H, m), 2.06–1.98 (1H, m) and 1.77–1.50 (3H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.80, 158.70, 134.32, 128.78 (2C), 114.34 (2C), 73.80, 55.27, 51.62, 48.18, 39.22, 33.90, 30.96 and 26.04; *m/z* (EI) 264 ( $\text{M}^+$ , 5%), 246 ( $\text{M}^+ - \text{H}_2\text{O}$ , 51), 135 (90) and 121 (100); (HRMS [ $\text{M}^+$ ], Found: 264.1363.  $\text{C}_{15}\text{H}_{20}\text{O}_4$  requires *M*, 264.1362).

#### Baeyer–Villiger oxidation of **1f** and hydrolysis to **4f** and **5f**

The reaction performed as described above, furnished the lactones **2f**:**3f** (52:48; quant. yield) which on hydrolysis and chromatography gave **4f** and **5f** (92%). *Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-(4-fluorophenyl)cyclohexanecarboxylate **4f**, mp 132–133 °C,  $\nu_{\max}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$  3422 (OH) and 1732 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.19–7.10 (2H, m, ArH), 7.0–6.90 (2H, ArH), 4.23–4.19 (1H, m), 3.43 (3H, s,  $\text{OCH}_3$ ), 3.29 (1H, td, *J* 12.1, 3.6), 2.55 (1H, td, *J* 11.6, 3.6) and 2.17–1.57 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  175.09, 161.51 ( $^1J_{\text{CF}}$  242.6), 139.60, 128.78 (2C,  $^3J_{\text{CF}}$  7.75), 115.20 (2C,  $^2J_{\text{CF}}$  21), 65.71, 51.36, 50.14, 40.28, 39.08, 31.61 and 23.78; *m/z* (EI) 252 ( $\text{M}^+$ , 2%), 234 ( $\text{M}^+ - 18$ , 100) and 175 (80); (HRMS [ $\text{M}^+$ ], Found: 252.1162.  $\text{C}_{14}\text{H}_{17}\text{O}_3\text{F}$  requires *M*, 252.1165).

*Methyl* (4S\*,1R\*,3R\*)-4-hydroxy-3-(4-fluorophenyl)cyclohexanecarboxylate **5f**,  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3425 (OH) and 1730 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.25–7.19 (2H, m, ArH), 7.07–6.98 (2H, m, ArH), 3.73 (3H, s), 3.70–3.58 (1H, m), 2.77–2.66 (2H, m), 2.34–2.21 (2H, m), 2.05–1.97 (1H, m) and 1.74–1.49 (3H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  176.77, 161.33 ( $^1J_{\text{CF}}$  244.7), 138.15, 129.28 (2C,  $^3J_{\text{CF}}$  7.8), 115.59 (2C,  $^2J_{\text{CF}}$  21.29), 73.92, 51.79, 48.23, 39.08, 33.90, 31.12 and 26.01; *m/z* (EI) 252 ( $\text{M}^+$ , 2%), 234 ( $\text{M}^+ - 18$ , 6), 174 (100) and 109 (62).

#### Baeyer–Villiger oxidation of **1g** and hydrolysis to **4g** and **5g**

The reaction performed as described above, furnished the bicyclic lactones **2g**:**3g** (70:30; 90%) which upon hydrolysis and chromatography gave **4g** and **5g** (82%). *Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-(2-nitrophenyl)cyclohexanecarboxylate **4g**,  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3447 (OH) and 1730 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.72–7.27 (4H, series of m), 4.27 (1H, m), 3.95–3.82 (1H, m), 3.43 (3H, s,  $\text{OCH}_3$ ) 2.74 (1H, td, *J* 11.6, 3.6), 2.38 (1H, br s, exchangeable) and 2.24–1.58 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.15, 150.53, 138.23, 132.43, 128.02, 127.07, 124.05, 65.40, 51.56, 49.12, 40.15, 34.07, 31.46 and 24.14; *m/z* (EI) 280 ( $\text{M}^+ + 1$ , 1%), 262 ( $\text{M}^+ - \text{H}_2\text{O}$ , 3), 233 ( $\text{M}^+ - \text{NO}_2$ , 100); (HRMS [ $\text{M}^+ - 33$ ], Found: 233.1178.  $\text{C}_{14}\text{H}_{17}\text{O}_3$  requires *M*, 233.1182).

*Methyl* (4S\*,1R\*,3R\*)-4-hydroxy-3-(2-nitrophenyl)cyclohexanecarboxylate **5g**,  $\nu_{\max}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$  3437 (OH) and 1726 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  7.76–7.38 (4H, series of m), 3.78 (3H, s), 3.8–3.75 (1H, m), 3.31–3.20 (1H, m), 2.78 (1H, m), 2.47–2.32 (3H, series of m) and 2.09–2.05 (2H, m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  169.18, 151.82, 136.88, 134.61, 131.40, 127.86, 127.28, 73.58, 51.88, 49.10, 42.96, 38.88, 32.19 and 25.96; *m/z* (EI) 233 ( $\text{M}^+ - \text{NO}_2$ , 100%).

#### Baeyer–Villiger oxidation of **1h** and hydrolysis to **4h** and **5h**

The reaction performed as described above, furnished the lactones **2h**:**3h** (75:25; 93%) which on hydrolysis and chromatography gave **4h** and **5h** (82%). *Methyl* (1S\*,2S\*,4R\*)-4-hydroxy-2-(4-nitrophenyl)cyclohexanecarboxylate **4h**, mp 131–132 °C;  $\nu_{\max}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$  3455 (OH) and 1732 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  8.05 (2H, d, *J* 8), 7.29 (2H, d, *J* 8), 4.22–4.17 (1H, m), 3.46–3.34 (1H, m), 3.36 (3H, s,  $\text{OCH}_3$ ), 2.56 (1H, td, *J* 11.6, 3.6) and 2.12–1.52 (6H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.48, 151.92, 146.76, 127.28 (2C), 123.74 (2C), 65.27, 51.48, 49.32, 39.94, 39.75, 31.67 and 23.72; *m/z* (EI) 79 ( $\text{M}^+$ , 11%), 261 ( $\text{M}^+ - 18$ , 15), 201 (98), 149 (49) and 116 (100); (HRMS [ $\text{M}^+$ ], Found: 279.1102.  $\text{C}_{14}\text{H}_{17}\text{NO}_5$  requires *M*, 279.1106).

*Methyl* (4S\*,1R\*,3R\*)-4-hydroxy-3-(4-nitrophenyl)cyclohexanecarboxylate **5h**,  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3524 (OH) and 1722 (ester);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  8.12 (2H, d, *J* 8, ArH), 7.36 (2H, d, *J* 8, ArH), 3.68 (3H, s), 3.72–3.65 (1H, m), 2.88–2.72 (2H, m), 2.33–2.18 (2H, m), 2.01–1.94 (1H, m) and 1.70–1.33 (3H, series of m);  $\delta_{\text{C}}(50.0 \text{ MHz}; \text{CDCl}_3)$  174.48, 150.75, 147.02, 128.72 (2C), 123.87 (2C), 73.48, 51.86, 48.79, 38.82, 33.66, 31.72, 26.03; *m/z* (EI) 279 ( $\text{M}^+$ , 10%), 261 (8), 201 (100), 149 (28), 128 (31) and 116 (85).

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