Baeyer–Villiger oxidation of norbornan-7-ones: long-range substituent effects on regioselectivity

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The regioselectivity of the Baeyer–Villiger oxidation of norbornan-7-ones can be steered by the distal 2-endo-substituents present. Hydrolysis of the resulting bicyclic lactones provides a stereospecific route to functionalized cyclohexanes.

Baeyer–Villiger (BV) oxidation is a commonly employed reaction for the transformation of ketones into esters/lactones by organic peroxy acids or hydrogen peroxide.¹ The BV reaction is extensively used since when it is suitably juxtaposed in a synthetic sequence, it can lead to the shortening of carbon chains, amplification of functionality in carbocyclic rings and chains, and transformation of carbocycles into heterocycles. Mechanistically, the reaction involves migration of one of the groups flanking the carbonyl to the adjacent electron-deficient oxygen atom in a concerted manner with retention of configuration.²⁻⁴ The migratory aptitude appears to be related to the ability of the group to support the developing positive charge in the transition state and this determines the regioselectivity of the reaction. Thus, the regiochemical outcome in BV oxidations is mainly governed by the nature of the α-substituent on the ketone although steric and conformational effects also play a role in some instances.⁵⁻⁷ Distal substituents, on the β or γ position to the carbonyl, have little influence on the regioselectivity. However, one example in the literature⁸ reports that regioselectivity in the BV oxidation of some 8-oxabicyclo[3.2.1]octan-3-ones is subject to long-range substituent effects. In connection with an ongoing project on the synthesis of carba-sugars,⁹ it was of interest to investigate the BV oxidation of several 2-endo-substituted norbornan-7-ones ¹ to give stereospecific access to trisubstituted cyclohexanes. During these studies, we have encountered a profound effect of the distal C(2)-endo-substituents on the migratory preferences of the apparently equivalent C(1)–C(7) and C(4)–C(7) bonds. Since this long-range steering of regioselectivity has potential synthetic utility and is governed by some subtle stereoelectronic effects, our observations are briefly reported here.

The 2-endo-substituted norbornan-7-ones 1a–h were synthesized according to the procedures previously described by us* and subjected to BV oxidation with m-chloroperbenzoic acid to furnish the lactones 2a–h (migration of back-bond ‘b’) and 3a–h (migration of bond ‘a’) in 85–95% yield (Scheme 1). The ratios of the two regiosomeric pair of lactones 2a–h and 3a–h were determined through 1H NMR integration of bridgehead protons at C(1) and C(4), which were very well separated at 200 MHz (see Scheme 1).

The structural identity of the lactones 2 and 3 was secured through base hydrolysis and diazomethane esterification to furnish the regiosomeric cyclohexane derivatives 4a–h and 5a–h, respectively, which were separated and fully characterized (¹H and ¹³C NMR, MS see Experimental section). The unambiguous evidence that enabled differentiation between the stereospecifically trifunctionalized cyclohexane 4a–h and 5a–h was deduced from the ¹H–¹H COSY spectra. There are three downfield signals due to H₃, H₄, and H₅ in the ¹H NMR spectra of 4 and 5 (Scheme 2) while in the regiosomers 4a–h, there is no coupling between H₃ and H₄ or H₅; the adjacent protons H₄ and H₅ are coupled. In a complementary way, in the series 5a–h, there is coupling between H₆ and H₇ but not between H₅ and H₆ or H₇.

The results presented in Scheme 1 indicate that the electron-withdrawing substituents (e.g., CN, CO₂Me, OMe, etc.) at the C-2 endo-position significantly diminish the propensity of the C(1)–C(7) bond to migrate vs. the C(4)–C(7) bond to the extent that in the case of 1a (R = CN) only the regiosomer 2a is formed with no trace of 3a being detected. In the case of 1b (R = CO₂Me), formation of the lactone 2b is overwhelmingly favoured over 3b. In the case of 1c, the 2-methoxy substituent exerts a somewhat moderate preference for the formation of 2c vs. 3c. These results can be understood in terms of the strong inductive effect exerted by the C-2 electron-withdrawing substituent, which is relayed to the C(1)–C(7) bond ‘a’ through the C(1)–C(2) bond. While the inductive effects of the α-substituents on the regioselectivity of BV oxidations are well documented, this is a rare example of dominant effect of the β-substituent on the migratory preferences.

The regioselectivity exhibited by the 2-endo-aryl derivatives 1d–h are also quite interesting, wherein the substituents in the remote phenyl ring lead to fine-tuning of the regioselectivity in a subtle manner. Surprisingly, the 2-endo-phenylnorbornan-7-
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 σ-electron acceptor and a through-space π-donor into the C(1)–(C2) σ-bond of 1d. Thus, the two effects are neutralized and the C(1)–(C2) bond is rendered equivalent to the C(3)–(C4) bond. Consequently, no regioselectivity is observed in the case of 1d. However, in the case of the α-nitrophenyl 1g and p-nitrophenyl 1h derivatives, the σ-bond acceptor ability is amplified but the through-space π-donor capacity is diminished. This renders the C(1)–(C2) bond electron deficient and, in turn, reduces the migratory propensity of the C(1)–(C7) 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 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. The key element in these interpretations is the ability of the C(1)–(C2) 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)–(C7) bond.

In summary, the regioselectivities in the BV oxidation of norbornan-7-ones can be profoundly influenced by the 2-endo-substituent (or absence thereof) and the 2-endo-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 1a and hydrolysis to 4a**

The reaction performed as described above, furnished the lactone 2a in quantitative yield. The lactone was hydrolysed to give 4a (90%). Methyl (1S*,2S*,4R*)-4-(hydroxy-2-methoxycyclohexa-1,2-dicarboxylate 4a, \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3437 (\text{OH}) \) and 1736 (ester); \( \delta_{\text{C}}(200 \text{ MHz; CDCl}_3) 174.80, 142.68, 128.69 (2\text{C}), 127.92 (2\text{C}), 126.84, 73.61, 51.67, 48.95, 39.12, 33.79, 31.09 and 26.01; \( \delta_{\text{H}}(200 \text{ MHz; CDCl}_3) 7.35–7.25 (5\text{H, m, ArH}), 3.75 (3\text{H, s, OCH}_3) 2.07–2.00 (1\text{H, m, and 1.81–1.52 (3\text{H, series of m;}) \delta_{\text{C}}(50.0 \text{ MHz; CDCl}_3) 172.59, 121.17, 64.21, 52.33, 44.74, 34.93, 31.24, 25.91 and 22.73; \nu_{\text{max}}(\text{EI}) 184 (M^+ + 1, 11%), 183 (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%; 98.5%) which on hydrolysis gave 4b (90%). Dimethyl (1S*,2S*,4R*)-4-(hydroxy-2-methoxycyclohexane-1,2-dicarboxylate 4b, \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3447 (\text{OH}) \) and 1736 (ester); \( \delta_{\text{C}}(200 \text{ MHz; CDCl}_3) 14.13 (1\text{H, br s}), 3.67 (6\text{H, s}), 3.12 (1\text{H, m}), 2.66 (1\text{H, m}), 2.10–2.04 (1\text{H, m} and 1.90–1.58 (5\text{H, series of m;}) \delta_{\text{C}}(50.0 \text{ MHz; CDCl}_3) 175.53, 174.92, 64.85, 51.80 (2\text{C}), 44.14, 39.17, 35.08, 31.60, 30.14 and 22.66; \nu_{\text{max}}(\text{EI}) 216 (M^+ , 1%), 184 (M^+ – 32, 138 (51), 97 (61) and 79 (100).

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

The reaction performed as described above, furnished the bicyclic lactones 2c–3c (77;23; 86%) which on hydrolysis yielded 4c (70%). Methyl (1S*,2S*,4R*)-4-(hydroxy-2-methoxycyclohexane-1,2-dicarboxylate 4c, \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3435 (\text{OH}) \) and 1736 (ester); \( \delta_{\text{C}}(200 \text{ MHz; CDCl}_3) 4.2–4.1 (1\text{H, m}), 3.88–3.76 (1\text{H, m}), 3.69 (3\text{H, s}), 3.31 (3\text{H, s}), 2.42 (1\text{H, td, J 9.4, 4}), 2.18–1.4 (6\text{H, series of m;}) \delta_{\text{C}}(50.0 \text{ MHz; CDCl}_3) 174.72, 76.19, 66.48, 56.59, 51.63, 48.20, 36.50, 31.66 and 22.55; \nu_{\text{max}}(\text{EI}) 188 (M^+ , 12%), 173 (9), 155 (16), 110 (33) and 87 (100); \nu_{\text{max}}(\text{HRMS} [M^+ – \text{CH}_2]); \text{Found: 173.0820. C}_{12} \text{H}_{16} \text{O}_{6} \text{ requires } M^+ , 173.0814).

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

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%).
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-methoxyphenyl)cyclohexanecarboxylate 5e, \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3445 (\text{OH}) \) and 1730 (ester); \( \delta_{q}(200 \text{ MHz; 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), 1.77–1.50 (3H, series of m); \( \delta_{q}(50.0 \text{ MHz; 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; \( \nu_{\text{m}}(\text{EI}) 264 (\text{M}^{+}, 5\%), 246 (\text{M}^{+} - \text{H}_{2}O, 51), 135 (90) and 121 (100); \) \( \text{HRMS} [\text{M}^+] \).

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

The reaction performed as described above, furnished the lactones 4g and 5g (22:78). Methyl (1S*,2S*,4R*)-4-hydroxy-2-(4-nitrophenyl)cyclohexanecarboxylate 4g, \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3447 (\text{OH}) \) and 1730 (ester); \( \delta_{q}(200 \text{ MHz; CDCl}_{3}) 7.27–7.19 (2H, m, ArH), 7.07–6.98 (2H, m, ArH), 3.73 (3H, s), 3.70–3.58 (1H, m), 2.77–2.67 (2H, m), 2.34–2.21 (2H, m), 2.05–1.97 (1H, m) and 1.74–1.49 (3H, series of m); \( \delta_{q}(50.0 \text{ MHz; CDCl}_{3}) 174.15, 150.53, 138.25, 132.43, 128.02, 127.07, 124.05, 65.40, 51.56, 49.12, 40.15, 34.07, 31.46 and 24.14; \( \nu_{\text{m}}(\text{EI}) 280 (\text{M}^{+} + 1, 1\%), 262 (\text{M}^{+} - \text{H}_{2}O, 3), 233 (\text{M}^{+} - \text{NO}_{2}, 100; \) \( \text{HRMS} [\text{M}^+] - 33) \).

Methyl (4S*,1R*,3R*)-4-hydroxy-3-(2-nitrophenoxy)cyclohexanecarboxylate 5g, \( \nu_{\text{max}}(\text{CHCl}_{3})/\text{cm}^{-1} 3437 (\text{OH}) \) and 1726 (ester); \( \delta_{q}(200 \text{ MHz; 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_{q}(50.0 \text{ MHz; 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; \( \nu_{\text{m}}(\text{EI}) 233 (\text{M}^{+} - \text{NO}_{2}, 100\%).

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References


