Epoxidation of 8a-Alkyl-1,2,3,4,6,8a-hexahydronaphthalen-1-ones and -1-ols

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Abstract: The regio- and diastereoselectivities of the epoxidations of decalin-1,4-dienes and dienols obtained from the Birch reductive alkylation of different α-tetralones is described. They appear to depend on the steric approach control of the peroxide and show an important contribution to the directing effect of homoallylic alcohols.

Key words: Birch alkylation, decalins, 1,4-dienes, epoxidation, directing effect

In connection with our project dealing with the synthesis of natural products,1 and taking into account, the importance of selective epoxidation of polyolefines in organic synthesis,2 we decided to explore the epoxidation of 1,4-dienes prepared by Birch reductive alkylation of substituted α-tetralones. Our goal was to control the stereochemistry in highly substituted decalin systems. Since we could not find any literature references on the epoxidation of such 1,4-dienes, it was necessary to search for the adequate conditions to carry out the epoxidation of these compounds in order to study their regio- and stereoselectivity.

In spite of the well known sensitivity of the 1,4-dienes to undergo acid-catalyzed rearrangements and reorganization, we choose m-chloroperbenzoic acid (m-CPBA) over dimethyldioxirane (DMDO), for the epoxidation, due to the better stereocontrol shown by the peracid.3 Therefore, it was necessary to select very carefully the reaction conditions in order to minimize the undesired rearrangements. We used the dienone 1a to optimize the procedure and tried mainly basic media due to the characteristics of the substrate [m-CPBA, CH₂Cl₂, -20 °C with or without NaHCO₃ (solid);4 m-CPBA, CHCl₃, Na₂CO₃ (solid), 0 °C;5 MMPP, CH₂Cl₂, r.t.6]. All the methods gave low yields of the desired epoxides with predominant formation of rearromatization products. The best results were finally obtained when we used m-CPBA under a buffered heterogeneous system CH₂Cl₂/0.5 M NaHCO₃ (pH 8.3) at 4 °C,7 or even better, with a phosphate buffer (pH 8.0)8 and these conditions were then used all throughout this study (Scheme 1). The dienones 1a–e were prepared according to our previous work.9

The dienone 1a reacted regioselectively, as expected in accord with the literature precedents,10,11 through the more substituted double bond producing a diastereomeric α:β mixture of the mono epoxides in a 2.7:1 ratio. The moderate stereoselectivity found could be explained on account of the shape of the dienone, which is almost planar, because the axial substituent creates steric hindrance making the approach of the peroxide more difficult towards this face. A similar stereochemical course of the reaction was observed in the photooxygenation reaction of dienone 1a where we obtained a mixture α:β (1.9:1) of allylic alcohols.12

A semiempirical study (AM1)13 of the epoxides reveals a difference of 1.88 kcal/mol in the heat of formation, favoring the β-isomer, showing that ratio of the products is kinetically controlled.

Table 1 lists the results obtained for all the ketones. As can be seen, the reaction with the dienone 1b occurs with the same stereo- and regioselectivity as for the dienone 1a. We found that the presence of the angular ether does not contribute to a better approach of the reagent to the β-face,14 indicating that it has a poor directing effect for

More text...
the peracid. On the other hand, in the case of the dienone 1e, the stereoselectivity was complete. We assume that probably the \( \pi \)-stacking of the allyl group with the diene hinders the \( \beta \)-face, allowing the approach of the peroxide only from the \( \alpha \)-face.

The dienones 1d and 1e gave mixtures of mono- and diepoxides. The regioselectivity of the system seemed to be lost perhaps due to the fact that both double bonds are now trisubstituted. So far we could not find adequate conditions to obtain the monoepoxides.

Surprisingly, the main products from the reaction of the dienones 1f and 1g were not the expected epoxides, but mixtures of the allylic alcohols 2f and 2g, respectively (Scheme 2). Thus, dienone 1f under the previously described conditions furnished, after column chromatography, the \( \alpha \)-allylic alcohol 2fa (20%), the \( \beta \)-allylic alcohol 2fb (12%) and the rearomatization product 2h (63%).

\[
\text{Scheme 2} \quad \text{i) m-CPBA, CH}_2\text{Cl}_2, 0.5 \text{ M NaHCO}_3, 4 \text{ °C, overnight}
\]

Similarly, the dienone 1g gave the \( \alpha \)-allylic alcohol 2ga (22.5%), the \( \beta \)-allylic alcohol 2gb (12.5%) and the rearomatization product 2h (54%). These results, although unexpected, can be explained as a radical-mediated competition process, similar to those leading to the rearomatization products, where the incipient radical formed may extract an hydroxyl radical from the peracid to produce the alcohols or to initiate the rearomatization process.

Finally, in an attempt to improve the diastereoselectivity of the epoxidation and also to determine the importance of the directing effect of the hydroxyl group toward the peracid approach, we devoted some effort to study the stereochemical course of the epoxidation of the dienols. Thus, the required alcohols were synthesized by selective reduction of the ketone and the epoxidation was carried out using the same conditions as for the ketones (Scheme 3).

\[
\text{Scheme 3} \quad \text{i) m-CPBA, CH}_2\text{Cl}_2, 0.5 \text{ M NaHCO}_3, 4 \text{ °C, overnight}
\]

The results obtained in the reactions using alcohols with different stereochemistries and axial substituents are given in Table 2. Table 2 shows that the \( \alpha \)-homoallylic alcohols 3a and 3b exert noticeable directing effect over the peracid improving the stereoselectivity of the addition by two or three fold compared with that of the related ketones, as had been previously observed in homoallylic alcohols. On the other hand, \( \beta \)-alcohols seemed to have no effect on diastereoselectivity. As expected, for 3d the \( \alpha \)-epoxide was the only product obtained.

In conclusion, we have studied the epoxidation reaction of several dienones, products of the Birch alkylation reaction of \( \alpha \)-tetralones, in order to see how nonbonding interactions affect the stereochemical course of the reaction. The reaction showed a complete regioselectivity and some degree of stereoselectivity. This regioselectivity is based in the greater speed of reaction of trisubstituted double bonds. We also established how the nature of the axial substituent of the diene affects the selectivity of the reaction showing that the nature of the substituent is more important than its size. We also have examined the directing effect of different homoallylic alcohols and, as expect-
Table 3  Spectral Data for Ketones 2a–c

<table>
<thead>
<tr>
<th>Product</th>
<th>$^1$H NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>$^1$C NMR (CDCl₃/TMS) δ</th>
<th>IR (film) v (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2aβ</td>
<td>5.50 (s, 2 H, H-7, 8), 3.15 (br s, 1 H, H-5), 1.40 (s, 3 H, 8a-CH₃)</td>
<td>211.66 (C=O), 127.62 (C-8), 120.26 (C-7), 62.82 (C-4a), 59.71 (C-5), 51.14 (C-8a), 37.17 (C-6), 30.34 (C-2), 25.66 (C-4), 21.87 (8a-CH₃), 19.91 (C-3)</td>
<td>2980, 1720, 1640, 1420, 1380, 1134, 875</td>
</tr>
<tr>
<td>2aα</td>
<td>6.05 (dd, 1 H, H-8), 5.38 (m, 1 H, H-7), 3.23 (q, 1 H, H-5), 1.38 (s, 3 H, 8a-CH₃)</td>
<td>210.20 (C-1), 127.42 (C-8), 119.45 (C-7), 65.41 (C-4a), 57.80 (C-5), 50.45 (C-8a), 36.97 (C-6), 28.03 (C-2), 25.49 (C-4), 24.17 (8a-CH₃), 21.04 (C-3)</td>
<td>2980, 1720, 1640, 1380, 1134, 875</td>
</tr>
<tr>
<td>2bβ</td>
<td>5.59 (br s, 2 H, H-7, 8), 3.78 (d, 1 H, J = 8.6, CH₃OCH₃), 3.46 (d, 1 H, J = 8.6, CH₃OCH₃), 3.33 (s, 3 H, OCH₃), 3.09 (dd, 1 H, J = 1.4 and 2.5, H-5), 2.8–2.4 (m, 3 H, H-2,3), 2.53 (br m, 2 H, H-6), 2.02–1.70 (m, 2 H, H-4), 1.39 (dt, 1 H, J = 6.3)</td>
<td>210.25 (C-1), 123.88 (C-8), 121.95 (C-7), 76.97 (CH₃OCH₃), 61.64 (C-4a), 59.23 (C-5), 59.14 (OCH₃), 55.45 (C-8a), 39.75 (C-6), 31.83 (C-2), 25.68, (C-4), 19.84 (C-3)</td>
<td>3020, 2920, 2010, 1710, 1700, 1495, 1415, 1310, 1215, 1190, 1125, 955, 895</td>
</tr>
<tr>
<td>2bα</td>
<td>6.02 (dt, 1 H, J = 10.8, H-8), 5.55 (m, 1 H, J = 10.8, H-7), 3.58 (dd, 2 H, J = 15.0 and 9.1, CH₃OCH₃), 3.32 (s, 3 H, OCH₃), 3.26 (dd, 1 H, J = 3.8 and 1.9, H-5), 2.45–2.70 (m, 5 H, H-2,3,6), 1.36 (dt, 1 H, J = 14, H-3), 2.20–2.00 (m, 2 H, H-4)</td>
<td>208.20 (C-1), 124.56 (C-8), 122.24 (C-7), 76.64 (CH₃OCH₃), 63.96 (C-4a), 59.44 (OCH₃), 58.07 (C-5), 56.47 (C-8a), 38.59 (C-6), 28.53 (C-2), 26.04 (C-4), 20.85 (C-3)</td>
<td>3030, 2920, 2815, 1705, 1600, 1450, 1310, 1250, 1195, 1100, 900, 840</td>
</tr>
<tr>
<td>2c</td>
<td>5.96 (dd, 1 H, J = 10.4, 2.5, H-7), 5.65–5.47 (m, 2 H, CH₂CH=CH₂ and H-8), 5.16 (dd, 1 H, J = 10.9 and 2.0, CH₂CH=CH₂), 5.07 (br d, 1 H, J = 1.8, CH₂CH=CH₂), 3.20 (dd, 1 H, J = 2.2 and 1.8, H-5), 2.69–2.40 (m, 5 H, H-2, 6 and CH₂CH=CH₂), 2.12 (m, 3 H, H-3, 4), 1.34 (dd, 1 H, J = 14.0 and 1.6, H-3)</td>
<td>208.97 (C-1), 131.82 (CH₂CH=CH₂), 125.29 (C-7), 121.25 (C-8), 118.51 (CH₂CH=CH₂), 64.32 (C-4a), 58.25 (C-5), 54.76 (C-8a), 41.36 (CH₂CH=CH₂), 37.30 (C-6), 28.10 (C-4), 26.29 (C-2), 20.99 (C-3)</td>
<td>2947, 1717, 1687, 1431, 1285, 1226, 904, 765</td>
</tr>
</tbody>
</table>

Melting points were determined on Ernst Leitz hot-stage microscope and are uncorrected. IR were recorded on a Bruker FT-IR spectrophotometer. $^1$H and $^1$C NMR spectra were measured at 200.1 MHz and 50.3 MHz on a Bruker AC 200-E NMR spectrometer in CDCl₃ solutions. 2D NMR experiments were run using standard Bruker software. Mass spectrometric analyses were obtained at UNICAMP-Brazil and University of California-Riverside Mass Spectrometry on homogenous samples verified by TLC on three solvent systems. All reactions were carried out under dry, oxygen-free N₂. TLC analyses were performed on aluminum foil plates coated with 0.1 mm Merck silica gel 60 GF 254 . Compounds that did not absorb UV light were visualized dipping in an anisaldehyde solution followed by heating. Column chromatography was run on Merck silica gel 60 H, under a low pressure of N₂, using increasing EtOAc/hexane gradients as solvent. All solvents were dried and distilled before use. For naming and describing the spectral data of the compounds, we used the numbering of base compounds derived from naphthalene.

**Epoxidation of 1,4-Dienones 1 and -Dienols 3 with m-CPBA; General Procedure**

Solid m-chloroperbenzoic acid (60%, 1.2 mmol) was slowly added in small portions to a magnetically stirred mixture of dienone 1 or dienol 3 (1 mmol) in CH₂Cl₂ (10 mL/mmol) andaq 0.5 M NaHCO₃ solution (5 mL/mmol, pH 8.5). The mixture was stirred at 4°C overnight and two of the phases were separated. The aqueous phase was diluted withaq 0.5 M NaHCO₃ solution and extracted with CH₂Cl₂ (3 × 10 mL). The organic phase was washed successively withaq 1 N NaOH solution (30 mL), H₂O (30 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to yield the crude product, which was purified by flash column chromatography (hexane/EtOAc). IR, $^1$H and $^1$C NMR data of all the products are listed in Tables 3 and 4.

4a,5β-Epoxy-8a-β-methyl-1,2,3,4,4a,5,6,8a-octahydroporphthenal-1-one (2αa) and 4a,5β-Epoxy-8a-β-methyl-1,2,3,4,4a,5,6,8a-octahydroporphthenal-1-one (2αβ)

Ketone 1a (1.5 g; 9.26 mmol) yielded 820 mg (60 %) of a mixture of 2αβ (28 %) and 2βα (72 %) as an oil.

**EIMS**: $m/z$ (%) = 178 (M⁺, 4), 135 (100), 118 (36), 108 (100), 91 (100), 77 (68), 55 (40), 39 (50).

**HRMS**: m/z calcd for C₁₂H₁₆O₃: 208.10994; Found: 208.10987.

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Table 4 Spectral Data of Ketones 4a-e

<table>
<thead>
<tr>
<th>Product</th>
<th>$^1$H NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>$^{13}$C NMR (CDCl₃/TMS) δ</th>
<th>IR (film) ν (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>5.44 (m, 2 H, H-7, 8), 3.71 (d, 1 H, J = 7.4, H-1), 3.06 (dd, 1 H, H-5), 2.85 (d, 1 H, OH, J = 7.4), 1.16 (s, 3 H, 8a-CH₃)</td>
<td>132.27 (C-8), 120.60 (C-7), 75.90 (C-1), 64.33 (C-4a), 56.73 (C-5), 40.66 (C-8a), 28.80 (C-6), 28.13 (C-2), 25.61 (C-4), 22.85 (8a-CH₃), 17.52 (C-3)</td>
<td>3439, 2937, 1654, 1430, 1278, 1152, 1059, 898</td>
</tr>
<tr>
<td>4b</td>
<td>5.70 (dt, 1 H, J = 10.25, H-8), 5.15 (dt, 1 H, J = 10.25, H-7), 3.61 (br t, 1 H, J = 1.82, H-1), 3.11 (d, 1 H, H-5), 1.18 (s, 3 H, 8a-CH₃)</td>
<td>130.91 (C-8), 124.72 (C-7), 73.31 (C-1), 61.70 (C-4a), 59.92 (C-5), 42.49 (C-8a), 30.97 (C-6), 26.64 (C-2), 26.18 (C-4), 19.95 (8a-CH₃), 19.06 (C-3)</td>
<td>3442, 2935, 1672, 1420, 1269, 1152, 1053, 865</td>
</tr>
<tr>
<td>4c</td>
<td>3.68 (dd, 1 H, J = 10.7 and 4.8, H-1), 3.12 (dd, 131.0 (C-8), 118.6 (C-7), 72.07 (C-1), 64.88 (C-4a), 58.23 (C-5), 41.52 (C-8a), 29.91 (C-6), 29.52 (C-2), 25.87 (C-4), 20.56 (C-3), 16.33 (8a-CH₃), 22.52 (C-2), 27.62 (C-4), 20.92 (C-3), 14.20 (8a-CH₃)</td>
<td>3395, 2929, 1642, 1442, 1265, 1152, 1067, 883</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>3.55 (dd, 1 H, J = 10.7 and 4.0, H-1), 3.08 (dd, 132.7 (C-8), 119.69 (C-7), 77.25 (C-1), 63.44 (C-4a), 59.70 (C-5), 42.23 (C-8a), 30.49 (C-6), 28.62 (C-2), 26.20 (C-4), 20.92 (C-3), 14.20 (8a-CH₃)</td>
<td>3395, 2929, 1642, 1442, 1265, 1152, 1067, 883</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>5.61 (dddd, 1 H, J = 1.7, 2.9, 4.5 and 10.3, H-7), 5.43 (dt, 1 H, J = 1.6 and 10.3, H-8), 3.82 (dt, 1 H, J = 3.0 and 8.0, H-1), 3.60 (d, 1 H, J = 8.6, CH₂CH₃), 3.34 (d, 1 H, J = 8.6, CH₂CH₃), 3.32 (s, 3 H, OCH₃), 3.11 (dd, 1 H, J = 3.8 and 1.9, H-5), 2.94 (d, 1 H, J = 8.1, OH), 2.52 (m, 2 H, H-6), 2.14 (dt, 1 H, H-3), 1.65 (m, 2 H, H-2), 2.04 (m, 2 H, H-4), 1.15 (br d, 1 H, J = 9.5, H-3)</td>
<td>129.09 (C-8), 123.40 (C-7), 76.05 (CH₂OCH₂), 71.79 (C-1), 62.60 (C-4a), 59.42 (OCH₃), 57.34 (C-5), 45.49 (C-8a), 28.83 (C-6), 26.67 (C-2), 26.12 (C-4) 17.18 (C-3)</td>
<td>3510, 2940, 1725, 1460, 1340, 1290, 1205, 1150, 1010, 990, 860</td>
</tr>
<tr>
<td>4f</td>
<td>5.78 (dm, 1 H, J = 10.4, H-7), 5.58 (dt, 1 H, J = 1.9, 10.4, H-8), 3.82 (dt, 1 H, J = 3.0 and 8.0, H-1), 3.73 (d, 1 H, J = 9.3, CH₂OCH₂), 3.46 (d, 1 H, J = 9.3, CH₂OCH₂), 3.35 (s, 3 H, OCH₃), 3.05 (dd, 1 H, J = 3.8 and 1.8, H-5), 2.94 (d, 1 H, J = 8.1, OH), 2.56 (m, 2 H, H-6), 2.14 (dt, 1 H, H-3), 1.90 (m, 2 H, H-4), 1.65 (m, 2 H, H-2), 1.13 (ddd, 1 H, J = 2.8, 4.6, 12.5 and H-3)</td>
<td>126.60 (C-8), 125.26 (C-7), 73.65 (CH₂OCH₂), 69.22 (C-1), 59.97 (C-4a), 59.39 (OCH₃), 58.78 (C-5), 46.59 (C-8a), 31.21 (C-6), 26.47 (C-2), 26.38 (C-4) 18.70 (C-3)</td>
<td>3475, 2929, 1460, 1151, 1048, 985, 878, 772</td>
</tr>
<tr>
<td>4g</td>
<td>5.70 (m, 1 H, J = 11.7, CH₂CH=CH₂), 5.54 (m, 1 H, H-7), 5.36 (dd, 1 H, J = 10.4 and 2.7, H-8), 5.10 (m, 1 H, J = 11.7, CH₂CH=CH₂), 5.04 (m, 1 H, CH₂CH=CH₂), 3.72 (dd, J = 2.9 and 8.0, H-1), 3.03 (dd, 1 H, J = 1.8 and 26.38 (C-2), 17.32 (C-3)</td>
<td>208.97 (C-1), 132.61 (CH₃CH=CH₂), 130.16 (C-7), 122.45 (C-8), 117.63 (CH₃CH=CH₂), 63.46 (C-4a), 57.22 (C-5), 44.13 (C-8a), 40.32 (CH₃CH=CH₂), 26.72 (C-6), 27.98 (C-4), 37.37 (H-5), 2.97 (d, 1 H, J = 8.0, OH), 2.51 (m, 2 H, CH₂CH=CH₂), 2.45–1.65 (m, 5 H, H-2, 3, 4), 1.09 (br d, 1 H, J = 11.1, H-3)</td>
<td>3554, 2947, 1643, 1431, 1285, 1002, 911, 845</td>
</tr>
</tbody>
</table>

* IR spectral data of a mixture of 4c and 4d.

8α-Allen-4a,5α-epoxy-1,2,3,4,6,8α-hexahydropthalen-1-one

2e Ketone 1c yielded 67.3 mg (62 %) of 2c as a colorless oil.

HRMS (EI): m/z calculated for C₂₃H₂₆O₂: 204.1150. Found: 204.1184. 4a,5α-Epoxy-8αβ-methyl-1,2,3,4,4a,5,6,8α-octahydropthalen-1α-ol (4a) and 4a,5α-Epoxy-8αβ-methyl-1,2,3,4,4a,5,6,8α-octahydropthalen-1α-ol (4b)

Dienol 3a (100 mg, 0.61 mmol) provided 4a (82 mg, 75 %) and 4b (17.3 mg, 16 %) as colorless oils.

4a

EIMS: m/z (%) = 180 (M⁺, 2.2 %), 162 (M⁺ – H₂O, 13.02), 118 (100).
Dienol 3b (185 mg, 1.13 mmol) gave a mixture of 4c and 4d (15:1 determined by NMR) as an oil (144 mg, 71 %).

Dienol 3c (100 mg, 0.51 mmol) yielded an oily mixture of 4e (82 mg, 75 %) and 4f (17.3 mg, 16 %).

Dienol 3b (185 mg, 1.13 mmol) yielded an oily mixture of 4e (82 mg, 75 %) and 4f (17.3 mg, 16 %).

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(6) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. Synthesis 1987, 1015.
(12) Unpublished results.
(13) Structures 2az and 2af were optimized with AM1 as implemented in HyperChem® 5.1, using an algorithm of conjugate gradient (Polak-Riviere).