DIASTEREOSELECTIVITY IN THE METHYLATION AND REDUCTION OF 3-ARYL-3a,4,5,6,7,7a-HEXAHYDRO-1,2-BENZISOXAZOL-4-ONES

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Abstracts- Various 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones were methylated at 3a-positions and reduced by NaBH₄ to afford the corresponding 3a,4-cis-3a,7a-cis-3a-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ols with excellent diastereoselectivity. The resulting hexahydro-1,2-benzisoxazol-4-ols were easily converted to the corresponding 2-aryl-2-methylcyclohexane-1,3-diols by catalytic hydrogenation with Raney Ni.

Isoxazolines prepared from the 1,3-dipolar cycloadditions of nitrile oxides with olefins are useful intermediates in organic synthesis due to their facile induction of stereocenters¹ and easy conversion of isoxazolines² to synthetically useful functional groups, such as β-hydroxy ketones,³,⁴ β-hydroxy amines,⁴ α,β-unsaturated ketones,⁴ substituted tetrahydrofurans.⁶ The 1,3-dipolar cycloaddition reactions of nitrile oxides with olefins exhibited regioselectivity by steric effect and electronic character of double bonds depending on the substituents on olefins. Although the 1,3-dipolar cycloaddition reactions of nitrile oxides with α,β-unsaturated ketones afforded a mixture of two regioisomers, the cycloadditions of aryl nitrile oxides to 2-cyclohexen-1-one could predominantly afford the corresponding 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones (1)⁷ together with 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-7-ones as minor regioisomers (around 10% of the major products). These regioisomers could easily be separated by silica gel column chromatography. The reduction of carbonyl group in the 3-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one by NaBH₄ gave a 1:1 mixture of diastereomers.⁸ We
examine the reduction of 1 (Ar=Ph) with various reducing agents such as NaBH₄, DIBAH, L-Selectride, and Super Hydride and the results are summarized in Scheme 1. When L-Selectride or Super Hydride was used as a reducing agent, only cis-isomer (2-cis) was diastereoselectively formed in good yield. The reduction using DIBAH proceeded very slowly and needed excess amounts of DIBAH (3 equiv.) with poor diastereoselectivity. The relative stereochemistry of 2-cis was supported by NOE experiment of ¹H NMR.

\[
\begin{array}{ccc}
\text{Reducing agent} & 2\text{-cis} & 2\text{-trans} \\
\text{NaBH₄} & 2/1 & \\
\text{DIBAH} & 1/1 & \\
\text{L-Selectride} & 99/1 & \\
\text{Super Hydride} & 99/1 & \\
\end{array}
\]

Scheme 1

It showed NOE at vicinal H-4 (5.7%, 4.24 ppm) and H-7a (5.9%, 4.45 ppm), when the doublet of doublet of H-3a at 3.43 ppm was irradiated, while 2-trans showed NOE only at H-7a (6.0%, 4.55 ppm) by the irradiation of the triplet of H-3a at 3.20 ppm.

Herein we wish to discuss mainly the diastereoselectivity in the methylation at 3a-position and reduction of carbonyl group of 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones (1). The methylations at 3a-position of 1 could be achieved by treatment with LDA followed by methyl iodide at 0 °C in THF and only cis-isomers (3) were formed in fairly good yields with no trace amount of trans-isomers. Carrying out the reaction at lower temperature or using excess base resulted in low yields due to the methylations at 5-position. The high diastereoselectivity in the methylation at 3a-position of isoxazolone (1) is caused by the retention of tetrahedral sp³ hybrid character of carbanion at C-3a after abstraction of hydrogen at 3a-position. The cis-configuration of methylated product (3a) could be confirmed by NOE experiment in ¹H NMR. Irradiation of H-7a at 4.70 ppm showed 10.06% of NOE at 1.51 ppm (3a-CH₃). On reduction of carbonyl groups of 3, we could isolate only 3a,4-cis-3a,7a-cis-4-hydroxy-3a,4,5,6,7,7a-hexahydrobenzisoxazoles (4) as a single diastereomer even when NaBH₄ was used as a reducing agent.
This suggests that the bottom-phase attack of reducing agent is disfavored due to bending-down the ring structure by the hindrance of 3a-methyl group together with the steric interaction of the aromatic ring. Actually, the angle of C3-C3a-C4 of 3a calculated by the MM' method is 114.438°, while the angle of C3-C3a-C4 of 1a is 115.556°, and the distance between the carbonyl carbon (C-4) and aryl-substituted carbon (C-3) of 3a is only 2.5 Å. The results obtained from methylation of 1 and reduction of 3 were summarized in Scheme 2 and Table 1.

The catalytic hydrogenation with Raney Ni3 of 4 provided the corresponding 2-aryl-2-methylocyclohexane-1,3-diols (5) in good yields as shown in Scheme 3. Since the structure of 1,3-diol (5a) has a symmetric plane, H-1 and H-3 appeared at the same position (4.41-4.37 ppm) in 1H NMR spectrum.

Table 1. Methylation and Reduction of 3-Aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones (1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>3 (Yield (%))</th>
<th>4 (Yield (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3a (76)</td>
<td>4a (92)</td>
</tr>
<tr>
<td>2</td>
<td>Cl-C6H4</td>
<td>3b (72)</td>
<td>4b (95)</td>
</tr>
<tr>
<td>3</td>
<td>Br-C6H4</td>
<td>3c (61)</td>
<td>4c (95)</td>
</tr>
<tr>
<td>4</td>
<td>F-C6H4</td>
<td>3d (74)</td>
<td>4d (91)</td>
</tr>
<tr>
<td>5</td>
<td>MeO-C6H4</td>
<td>3e (67)</td>
<td>4e (98)</td>
</tr>
</tbody>
</table>
and only ten carbon peaks were found in $^{13}$C NMR spectrum. After removal of OH peaks of 5a at 4.26 ppm by addition of D$_2$O, the irradiation of H-1 and H-3 at 4.39 ppm showed 3.36% NOE of 2-CH$_3$ at 1.19 ppm in $^1$H NMR. We could confirm the relative stereochemistry of three stereocenters of 5 by these NMR experiments.

In conclusion, from 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones prepared from the 1,3-dipolar cycloadditions of nitrile oxides with 2-cyclohexen-1-one, we could prepare the highly functionalized cyclohexanes via diastereoselective methylations and reductions followed by the reductive cleavage of the isoxazoline ring.

\[
\begin{array}{c}
\text{OH} \\
\text{Me} \\
\text{Ar} \\
\text{H} \\
\text{N}
\end{array}
\xrightarrow{\text{Raney Ni, H}_2} \quad \begin{array}{c}
\text{OH} \\
\text{Me} \\
\text{Ar} \\
\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{B(OH)$_3$, MeOH} \\
\text{rt, 1 h}
\end{array}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>97%</td>
</tr>
<tr>
<td>5c</td>
<td>87%</td>
</tr>
<tr>
<td>5e</td>
<td>88%</td>
</tr>
</tbody>
</table>

\textbf{Scheme 3}

\textbf{EXPERIMENTAL SECTION}

\textit{General} $^1$H NMR spectra, $^{13}$C NMR spectra, and spectra of NOE experiments were recorded on Bruker AM-300MHz using TMS as an internal standard. IR spectra were taken with Digilab FTs-80 or Digilab FTs-165 spectrophotometer. HRMS spectra were obtained by Jeol JMX-DX 303 mass spectrometer. Flash column chromatography was carried out on silica gel Merck (230-400 mesh). All chemicals and solvents except THF were directly used from commercial sources. THF was dried over potassium metal before use. Microanalyses were performed by the Organic Chemistry Research Center, Sogang University, Seoul.

\textbf{Reduction of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1) by sodium borohydride.}

To a solution of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one$^7$ (1, 0.5 g, 2.3 mmol) in methanol (20 mL) was added sodium borohydride (0.17 g, 4.6 mmol) portionwisely at 0 °C. After being stirred for 30 min, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by a rotary evaporator to give a mixture of 2-cis and 2-trans as an oily residue (0.47 g, 94%). The ratio of two diastereomers (2-cis : 2-trans) determined by $^1$H NMR spectrum was proved to be 2 : 1. The two
diastereomers were separated by silica gel column chromatography (n-hexane/EtOAc, 10/1) and confirmed by NOE experiments of $^1$H NMR.

3a,4-cis-3a,7a-cis-4-Hydroxy-3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (2-cis). Oil, $^1$H NMR (acetone-d$_6$): $\delta$ 7.78-7.74 (2H, m), 7.40-7.36 (3H, m), 4.46-4.43 (1H, m), 4.26-4.22 (1H, m), 3.43 (1H, dd, $J$=5.3, 8.4 Hz), 3.36-3.33 (1H, br m), 2.07-1.35 (6H, m); $^{13}$C NMR (acetone-d$_6$): $\delta$ 160.5, 130.0, 128.7, 128.3, 126.5, 79.6, 63.3, 49.6, 30.0, 24.1, 12.9; FT-IR (cm$^{-1}$): 3367, 2940, 2914, 1446, 1357, 1266, 1203, 1099, 980, 914, 761, 691; MS m/z (relative intensity): 218 (3.4), 217 (4.7), 146 (100.0), 145 (61.1), 77 (26.9); HRMS calcd for C$_{13}$H$_{15}$NO$_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.99; N, 6.42.

3a,4-trans-3a,7a-cis-4-Hydroxy-3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (2-trans). Oil, $^1$H NMR (CDCl$_3$): $\delta$ 7.98-7.84 (2H, m), 7.45-7.30 (3H, m), 4.61-4.52 (1H, m), 3.70-3.58 (1H, m), 3.20 (IH, t, $J$=7.7 Hz), 2.31-2.22 (1H, br m), 2.03-1.25 (6H, m); $^{13}$C NMR (acetone-d$_6$): $\delta$ 163.7, 130.1, 129.8, 128.6, 127.8, 82.2, 71.8, 52.7, 32.4, 24.7, 18.6; FT-IR (cm$^{-1}$): 3389, 2938, 2869, 1447, 1351, 1260, 1074, 914, 854, 767, 691; HRMS calcd for C$_{13}$H$_{15}$NO$_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.99; N, 6.42.

Reduction of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1) by DIBAH. To a solution of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1, 0.5 g, 2.3 mmol) in anhydrous THF (20 mL) was added DIBAH (1 M solution in THF, Aldrich, 3 mL, 3.0 mmol) by a syringe at 0°C. After stirring 3 h, the reaction mixture was poured into ice-cold aqueous 1 N HCl solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by a rotary evaporator to give an oily residue. The residue was separated by silica gel column chromatography (hexane/ethyl acetate, 5/1) to give 2-cis (0.12 g) and 2-trans (0.11 g) in 46% combined yield.

Reduction of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1) by L-Selectride. To a solution of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1, 0.5 g, 2.3 mmol) in anhydrous THF (20 mL) was added L-Selectride (1 M solution in THF, Aldrich, 2.53 mL, 2.53 mmol) by a syringe at 0°C. After stirring 30 min, the reaction mixture was poured into ice-cold aqueous 1 N HCl solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by a rotary evaporator to give only 2-cis as an oil (0.48 g, 96%). However 2-cis was very pure without any purification process, it could be more purified by silica gel chromatography (ethyl acetate/hexane, 1/5).

Reduction of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1) by Super Hydride. To a solution of 3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-one (1, 0.5 g, 2.3 mmol) in anhydrous
THF (20 mL) was added Super Hydride (1 M solution in THF, Aldrich, 2.53 mL, 2.53 mmol) by a syringe at -20 °C. After stirring 30 min, the reaction mixture was poured into ice-cold aqueous 1 N HCl solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by a rotary evaporator to give an oil. The oil was purified by silica gel chromatography (ethyl acetate/hexane, 1/5) to give only 2-cis as an oil (0.44 g, 88%).

General procedure for the preparation of 3a,7a-cis-3-aryl-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-ones (3). To a solution of 1 (5 mmol) in anhydrous THF (20 mL) was slowly added LDA (5.5 mmol, 2.75 mL of 2 M solution in THF, Aldrich) by a syringe at 0 °C. The solution was stirred for 0.5 h at 0 °C, and then iodomethane (0.343 mL, 5.5 mmol) was added. After the reaction mixture was stirred further for 3 h at 25 °C, it was poured into ice-water and extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated to give oily residue. The major product was separated by silica gel column chromatography (ethyl acetate/hexane, 1/10) to give 3 which was identified by 'H NMR, 13C NMR, FT-IR, and HRMS, additionally for 3a, elemental analysis was obtained.

3a,7a-cis-3a-Methyl-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3a). oil, 76%, 'H NMR (CDCl$_3$): δ 7.38-7.32 (3H, m), 7.19-7.12 (2H, m), 4.70 (1H, dd, J=2.8, 5.6 Hz), 2.45-1.66 (6H, m), 1.51 (3H, s); 13C NMR (CDCl$_3$): δ 209.8, 158.2, 130.1, 128.4, 128.3, 126.9, 91.8, 64.2, 38.9, 25.5, 20.2, 19.2; FT-IR (cm$^{-1}$): 2939, 2874, 1712, 1449, 1313, 935, 767; HRMS calcd for C$_{14}$H$_{16}$NO, M+ found 229.1096. Anal. Calcd for C$_{14}$H$_{16}$NO: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.38; H, 6.56; N, 6.09.

3a,7a-cis-3-(4-Chlorophenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3b). oil, 72%, 'H NMR (CDCl$_3$): δ 7.62 (2H, d, J=8.6 Hz), 7.32 (2H, d, J=8.6 Hz), 4.70 (1H, dd, J=4.8, 5.7 Hz), 2.51-2.36 (2H, m), 2.23-1.99 (2H, m), 1.95-1.72 (2H, m), 1.53 (3H, s); 13C NMR (CDCl$_3$): δ 209.6, 157.6, 136.2, 129.3, 129.0, 128.7, 128.3, 126.9, 91.7, 63.9, 38.8, 27.2, 20.1, 19.13; FT-IR (cm$^{-1}$): 2946, 2876, 1712, 1493, 1094, 833; HRMS calcd for C$_{14}$H$_{16}$NOCl, M+ found 263.1094.

3a,7a-cis-3-(3-Bromophenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3c). oil, 61%, 'H NMR (CDCl$_3$): δ 7.91-7.89 (1H, m), 7.59-7.49 (2H, m), 7.28-7.17 (1H, m), 4.70 (1H, dd, J=4.74, 5.70 Hz), 2.52-2.01 (2H, m), 1.93-1.73 (4H, m), 1.52 (3H, s); 13C NMR (CDCl$_3$): δ 209.4, 157.5, 133.0, 130.4, 130.2, 129.9, 125.4, 122.8, 91.7, 63.72, 38.8, 27.1, 20.0, 19.1; FT-IR (cm$^{-1}$): 2949, 2875, 1713, 1546, 1313, 1075, 496, 789; HRMS calcd for C$_{14}$H$_{16}$NOBr, M+ found 307.0203.

3a,7a-cis-3-(2-Fluorophenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3d). oil, 74%, 'H NMR (CDCl$_3$): δ 7.52-7.34 (2H, m), 7.21-7.06 (2H, m), 4.69 (1H, dd, J=4.6, 5.6 Hz), 2.49-2.43 (2H, m), 2.19-1.78 (4H, m), 1.43 (3H, s); 13C NMR (CDCl$_3$): δ 208.1, 161.7, 158.4, 156.1, 131.6, 130.5,
124.1, 116.3, 90.2, 64.8, 38.6, 26.6, 19.7, 19.0; FT-IR (cm\(^{-1}\)): 3071, 2950, 2877, 1712, 1585, 1493, 1222, 1106, 761; HRMS calcd for C\(_{14}\)H\(_{14}\)NO\(_2\)F 247.1008, found 247.0988.

3a,7a-cis-3-(4-Methoxyphenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole-4-one (3e). oil, 67%, \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.68 (2H, d, \(J=4.3\) Hz), 6.88 (2H, d, \(J=4.4\) Hz), 4.54 (1H, m), 3.81 (3H, s), 2.62-1.81 (6H, m), 1.51 (3H, s); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 210.1, 161.0, 157.7, 128.4, 120.8, 114.3, 91.5, 64.3, 55.3, 39.0, 27.8, 20.3, 19.2; FT-IR (cm\(^{-1}\)): 2968, 2932, 1707, 1514, 1253, 1178, 1030, 939, 836; HRMS calcd for C\(_{14}\)H\(_{14}\)NO\(_2\) 259.1208, found 259.1215.

General procedure for the preparation of 3a,4-cis-3a,7a-cis-3-aryl-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazoles (4). To a solution of 3 (5 mmol) in 95% methanol (20 mL) was slowly added NaBH\(_4\) (0.284 g, 7.5 mmol) in a small portions at 0 °C. The reaction mixture was stirred for 1 h at 25 °C, and it was poured into ice-water and then extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated to give pure 4 which could be identified without any purification procedure. The product (4) was identified by \(^1\)H NMR, \(^{13}\)C NMR, FT-IR, and HRMS, additionally for 4a, elemental analysis was obtained.

3a,4-cis-3a,7a-cis-4-Hydroxy-3a-methyl-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole (4a). oil, 92%, \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.65-7.62 (2H, m), 7.43-7.26 (3H, m), 4.19 (IH, s), 3.99-3.95 (IH, m), 2.30-1.47 (6H, m), 1.31 (3H, s); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 164.8, 129.8, 128.7, 127.2, 85.4, 77.4, 77.0, 76.6, 70.0, 54.7, 27.8, 23.1, 19.7, 13.2; FT-IR (cm\(^{-1}\)): 3345, 2932, 1460, 1058, 892, 769, 670; HRMS calcd for C\(_{14}\)H\(_{14}\)NO\(_2\) 231.1259, found 231.1260. Anal. Calcd for C\(_{14}\)H\(_{14}\)NO\(_2\): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.47; N, 5.95.

3a,4-cis-3a,7a-cis-3-(4-Chlorophenyl)-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole (4b). oil, 95%, \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.61-7.26 (4H, m), 4.19 (1H, m), 1.89-1.46 (7H, m), 1.30 (3H, s); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 164.0, 128.9, 128.5, 128.4, 85.6, 77.4, 77.0, 76.6, 70.0, 54.6, 27.8, 23.0, 19.7, 13.2; FT-IR (cm\(^{-1}\)): 3376, 2944, 2873, 1434, 1326, 1057, 893, 766; HRMS calcd for C\(_{14}\)H\(_{14}\)NO\(_2\)Cl 265.7402, found 265.7386.

3a,4-cis-3a,7a-cis-3-(3-Bromophenyl)-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole (4c). oil, 95%, \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.80 (1H, m), 7.59-7.25 (3H, m), 4.19 (1H, m), 1.89-1.46 (7H, m), 1.30 (3H, s); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 163.7, 132.7, 130.1, 125.8, 85.7, 77.4, 77.0, 76.6, 70.0, 54.7, 27.9, 23.0, 19.6, 13.1; FT-IR (cm\(^{-1}\)): 3534, 3373, 2943, 2873, 1434, 1326, 1057, 893, 766; HRMS calcd for C\(_{14}\)H\(_{16}\)NO\(_2\)Br 310.1910, found 310.1904.

3a,4-cis-3a,7a-cis-3-(2-Fluorophenyl)-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole (4d). oil, 91%, \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.62-7.50 (1H, m), 7.42-7.36 (1H, m), 7.18-7.01 (2H, m), 4.19-4.15
(1H, m), 3.88-3.72 (1H, m), 2.35-2.08 (2H, m), 1.35-1.89 (5H, m), 1.16 (3H, s); 13C NMR (CDCl3): δ 206.3, 131.8, 124.8, 116.7, 116.4, 86.5, 70.0, 56.6, 30.1, 29.8, 29.5, 24.6, 20.5, 19.9; FT-IR (cm⁻¹): 3452, 2943, 2880, 1453, 1221, 893; HRMS calcd for C₁₉H₁₈N⁰₂F 249.2859, found 249.2853.

3a,4-cis-3a,7a-cis-4-Hydroxy-3-(4-methoxyphenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazole (4e). oil, 98%, 1H NMR (CDCl₃): δ 7.57 (2H, d, J=8.9 Hz), 6.91 (2H, d, J=8.9 Hz), 4.13 (1H, t, J=3.3 Hz), 3.93-3.82 (1H, m), 3.80 (3H, s), 1.85-1.34 (7H, m), 1.28 (3H, s); 13C NMR (CDCl₃): δ 164.2, 160.7, 128.5, 122.2, 114.1, 85.2, 69.9, 55.2, 54.5, 27.7, 23.0, 19.8, 13.2; FT-IR (cm⁻¹): 3493, 2941-2880, 1610, 1513, 1250, 1035, 829; HRMS calcd for C₂₀H₂₀N⁰₂ 261.1365, found 261.1358.

**General procedure for the preparation of 1,2-cis-2,3-cis-2-aroyl-1,3-dihydroxy-2-methylcyclohexanes (5).** To a solution of 4 (2 mmol) in 10 mL of 80% methanol (methanol/water, 8:2) was added boric acid (0.25 g, 4 mmol) and Raney Ni (10-20 mg) at 25 °C. The reaction mixture was stirred vigorously for 1 h under hydrogen atmosphere (hydrogen balloon). The solution was filtered and the filtrate was diluted with water, and then extracted with methylene chloride (30 mL x 2). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated to give oily residue. The product (5) was separated by silica gel column chromatography (ethyl acetate/hexane, 1/10) and identified by 1H NMR, 13C NMR, FT-IR, and HRMS, additionally for 5a, elemental analysis was obtained.

1,2-cis-2,3-cis-2-Benzoyl-1,3-dihydroxy-2-methylcyclohexane (5a). oil, 97%, 1H NMR (CDCl₃): δ 7.76-7.71 (2H, m), 7.52-7.37 (3H, m), 4.41-4.37 (2H, m), 4.26 (2H, d, J=7.2 Hz), 2.06-1.44 (6H, m), 1.19 (3H, s); 13C NMR (CDCl₃): δ 211.7, 138.3, 130.9, 128.2, 127.5, 72.2, 55.2, 27.5, 19.6, 13.3; FT-IR (cm⁻¹): 3382, 2928, 2862, 1657, 1445, 1336, 234.1256, found 234.1250. Anal. Calcd for C₁₉H₁₆O₂: C, 71.77; H, 7.74. Found: C, 71.76; H, 7.78.

1,2-cis-2,3-cis-2-(3-Bromobenzoyl)-1,3-dihydroxy-2-methylcyclohexane (5c). oil, 87%, 1H NMR (CDCl₃): δ 7.91-7.26 (4H, m), 4.35-4.30 (2H, m), 4.17 (2H, d, J=7.1 Hz), 1.95-1.32 (6H, m), 1.16 (3H, s); 13C NMR (CDCl₃): δ 167.0, 140.2, 133.8, 130.5, 129.8, 126.0, 122.5, 73.4, 55.5, 27.5, 19.5, 13.3; FT-IR (cm⁻¹): 3317, 2950, 2862, 1657, 1445, 1336, 244, 993, 701; HRMS calcd for C₁₉H₂₄O₂Br 312.0361, found 312.0365.

1,2-cis-2,3-cis-1,3-Dihydroxy-2-(4-methoxybenzoyl)-2-methylcyclohexane (5e). oil, 88%, 1H NMR (CDCl₃): δ 7.60 (2H, d, J=9.1 Hz), 6.81 (2H, d, J=9.0 Hz), 4.44-4.10 (2H, m), 4.34 (2H, d, J=7.1 Hz), 3.83 (3H, s), 1.98-1.39 (6H, m), 1.25 (3H, s); 13C NMR (CDCl₃): δ 208.1, 162.2, 130.6, 129.8, 113.5, 72.9, 54.3, 54.6, 27.6, 20.0, 13.3; HRMS calcd for C₁₉H₂₀O₄ 264.1361, found 264.1359.
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REFERENCES


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