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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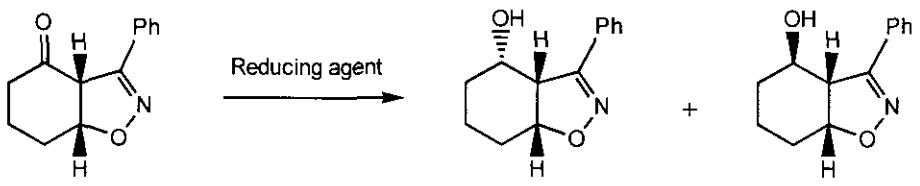
Abstracts- Various 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones were methylated at 3a-positions and reduced by $NaBH_4$ to afford the corresponding 3a,4-*cis*-3a,7a-*cis*-3a-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ols with excellent diastereoselectivity. The resulting hexahydro-1,2-benzisoxazol-4-ols were easily converted to the corresponding 2-aroyl-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 stereocenters[1] and easy conversion of isoxazolines[2] to synthetically useful functional groups, such as β-hydroxy ketones,[1f,3] β-hydroxy amines,[4] α,β-unsaturated ketones,[5] 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 $NaBH_4$ gave a 1:1 mixture of diastereomers.[1f] We

examined the reduction of **1** (Ar=Ph) with various reducing agents such as $NaBH_4$, 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.



1 **2-*cis*** **2-*trans***

Reducing agent	**2-*cis*/2-*trans***
$NaBH_4$	2/1
DIBAH	1/1
L-Selectride	99/1
Super Hydride	99/1

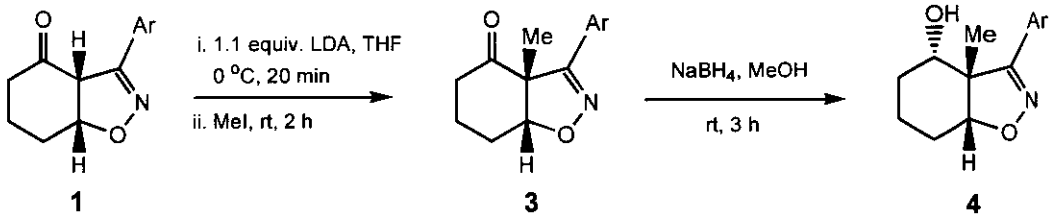
Scheme 1

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 sp^3 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-CH_3). 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 $NaBH_4$ was used as a reducing agent.

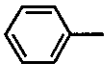
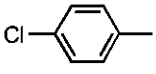
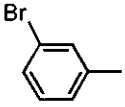
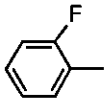
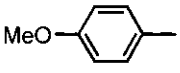
This suggests that the bottom-phase attack of reducing agent is disfavored due to bending–down the ring structure by the hindrance of 3a-methyl group together with the steric interaction of the aromatic ring. Actually, the angle of C3-C3a-C4 of **3a** calculated by the MM^+ method is 114.438 °, while 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 Ni[3] of **4** provided the corresponding 2-aroyl-2-methylcyclohexane-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 ^{1}H NMR spectrum



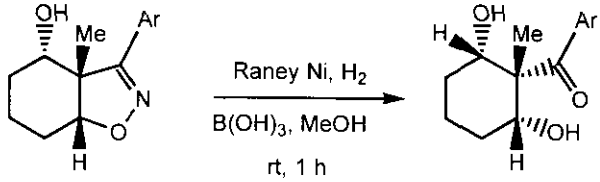
Scheme 2

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

Entry	Ar	**3** (Yield (%))	**4** (Yield (%))
1		**3a** (76)	**4a** (92)
2		**3b** (72)	**4b** (95)
3		**3c** (61)	**4c** (95)
4		**3d** (74)	**4d** (91)
5		**3e** (67)	**4e** (98)

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_2O, 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 ^1H 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.



4 **5**

Compound	Yield (%)
5a	97%
5c	87%
5e	88%

Scheme 3

EXPERIMENTAL SECTION

General ^1H 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.

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 ^1H 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): δ 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): δ 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, 1074, 980, 914, 889, 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 $C_{13}H_{15}NO_2$ 217.1102, found 217.1095. Anal. 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 ($CDCl_3$): δ 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 (1H, t, *J*=7.7 Hz), 2.31-2.22 (1H, br m), 2.03-1.25 (6H, m); ^{13}C NMR (acetone-d_6): δ 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, 1046, 916, 890, 854, 767, 691; HRMS calcd for $C_{13}H_{15}NO_2$ 217.1102, found 217.1101.

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 ^{1}H NMR, ^{13}C 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%, ^{1}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); ^{13}C 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 $C_{14}H_{15}NO_2$ 229.1103, found 229.1096. Anal. Calcd for $C_{14}H_{15}NO_2$: 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%, ^{1}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); ^{13}C 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 $C_{14}H_{14}NO_2Cl$ 263.0173, found 263.1094.

3a,7a-*cis*-3-(3-Bromophenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3c). oil, 61%, ^{1}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); ^{13}C 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 $C_{14}H_{14}NO_2Br$ 307.0208, found 307.0203.

3a,7a-*cis*-3-(2-Fluorophenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3d). oil, 74%, ^{1}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); ^{13}C 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 $C_{14}H_{14}NO_2F$ 247.1008, found 247.0988.

3a,7a-*cis*-3-(4-Methoxyphenyl)-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazol-4-one (3e). oil, 67%, ^1H NMR ($CDCl_3$): δ 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 ($CDCl_3$): δ 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 $C_{15}H_{17}NO_3$ 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 ^1H 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%, ^1H NMR ($CDCl_3$): δ 7.65-7.62 (2H, m), 7.43-7.26 (3H, m), 4.19 (1H, s), 3.99-3.95 (1H, m), 2.30-1.47 (6H, m), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$): δ 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 $C_{14}H_{17}NO_2$ 231.1259, found 231.1260. Anal. Calcd for $C_{14}H_{17}NO_2$: 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%, ^1H NMR ($CDCl_3$): δ 7.61-7.26 (4H, m), 4.19 (1H, m), 3.94-3.90 (1H, m), 1.89-1.46 (7H, m), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$): δ 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 $C_{14}H_{16}NO_2Cl$ 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%, ^1H NMR ($CDCl_3$): δ 7.80 (1H, m), 7.59-7.25 (3H, m), 4.19 (1H, m), 3.96-3.92 (1H, m), 1.89-1.56 (7H, m), 1.32 (3H, s); ^{13}C NMR ($CDCl_3$): δ 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, 1059, 898, 766; HRMS calcd for $C_{14}H_{16}NO_2Br$ 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%, ^1H NMR ($CDCl_3$): δ 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); ^{13}C NMR ($CDCl_3$): 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 $C_{14}H_{16}NO_2F$ 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%, ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $C_{15}H_{19}NO_3$ 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 ^{1}H NMR, ^{13}C 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%, ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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, 1244, 993, 701; HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1250. Anal. Calcd for $C_{14}H_{18}O_3$: 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%, ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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, 1667, 1599, 1252, 1175, 944, 846; HRMS calcd for $C_{14}H_{17}O_3Br$ 312.0361, found 312.0365.

1,2-*cis*-2,3-*cis*-1,3-Dihydroxy-2-(4-methoxybenzoyl)-2-methylcyclohexane (**5e**). oil, 88%, ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $C_{15}H_{20}O_4$ 264.1361, found 264.1359.

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