Selective Allylic Hydroxylation of Octahydronaphthalene Derivatives with a Bridgehead Double Bond Using Electrochemical Method with Iron Picolinate Complexes

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The combination of electrolysis and the $Fe^{III}(PA)_3/O_2/CH_3CN$ system was investigated for allylic hydroxylation of octahydronaphthalene derivatives. Substrates with a bridgehead double bond gave the allylic alcohol with α-preference, while non-bridgehead olefin did not react smoothly. This system is a useful tool for α-selective allylic hydroxylation of octahydronaphthalene derivatives with a bridgehead double bond as model compounds for the AB fused ring of cholesterols.

Key words allylic hydroxylation; iron catalysis; electrochemical oxidation; 7α-hydroxylation

Oxygenation reactions are very important in steroid metabolism and biosynthesis.[1—3] Many investigations on biomimetic oxygenation systems using iron(III) picolinate ($Fe^{III}(PA)_3$) or iron(II) picolinate ($Fe^{II}(PA)_2$) complexes as catalysts have been reported under various conditions and in various solvents,[4—8] but direct 7α-hydroxylation is not easy and most reported allylic hydroxylations involve multistep reactions *via* other functionalized compounds[9—14] or afford low yield or stereoselectivity.[15—17] We have been developing a 7α-hydroxylation system for steroids,[18—20] and we reported in a preceding paper that the combination of electrolysis and the $Fe^{III}(PA)_3/O_2/CH_3CN$ system gave good results in the hydroxylation of cholesteryl acetate.[21]

On the other hand, functionalization, especially oxygenation, of octahydronaphthalenes or decalin derivatives is also very important because many bioactive or natural compounds contain a skeleton resembling the AB fused ring of cholesterol.[22—24] Therefore, we wished to identify the required structural factors for regio- and stereoselective direct 7α-hydroxylation of steroids by our electrochemical method, as well as to extend the range of applicability of this method for allylic α-hydroxylation of small cyclic compounds.

In this report, we describe the iron picolinate-induced hydroxylation reactions of octahydronaphthalene derivatives **5b**, **6b** and **7b** as simple models for allylic oxygenation of steroids or other decalin derivatives.

Results and Discussion

The substrates **5b**—**7b** were prepared by benzoylation of the corresponding octahydronaphthalenols **5a**—**7a**.[25—27] Both **5b** and **6b** have an alkene moiety at a similar position to C5–C6 of cholesterol. However, the double bond of **7b** is not located at the bridgehead of the fused ring. We applied

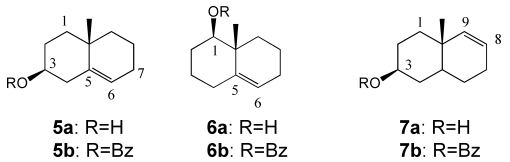

Fig. 1. The Substrates for Oxygenation Reactions

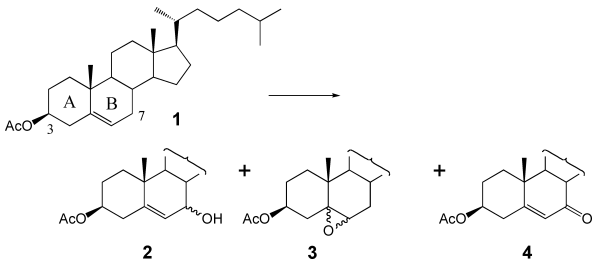

Chart 1. The Oxygenation of Cholesteryl Acetate

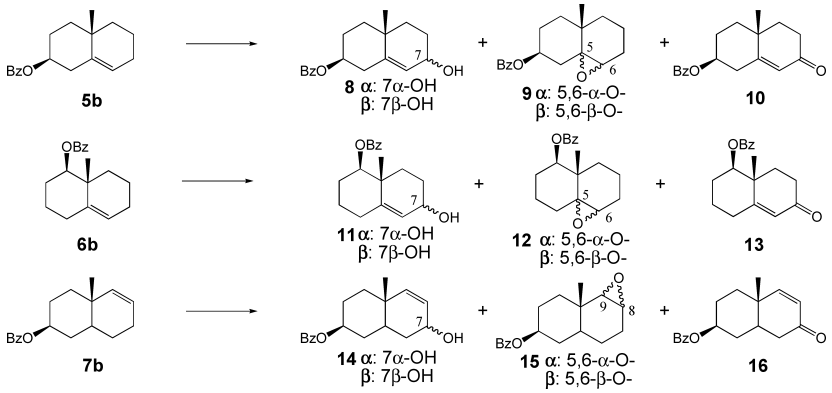

Chart 2. Oxygenation Reactions of Octahydronaphthalenes

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the combination of electrolysis and the $Fe^{III}(PA)_3/O_2/CH_3CN$ system to these substrates under reaction conditions similar to those we used previously for cholesteryl acetate. The substrate was dissolved in a solution of supporting electrolyte in acetonitrile, and the resulting solution was put into an H-shaped one-compartment glass cell equipped with platinum mesh electrodes. Oxygen gas was bubbled through the mixture with electrolysis at −0.1 V (*vs.* Ag/AgCl) and magnetic stirring for 1 h at room temperature (23 °C). The results are shown in Chart 2 and Table 1. As we reported before,[21] this condition is not effective for reduction of dioxygen and it permits the one-electron reduction of $Fe^{III}(PA)_3$ in acetonitrile. Furthermore, because significant amount of the substrates were recovered, it can be considered that overoxidation caused by disappearance of the substrates was avoided.

The reaction of substrate **5b** gave the allylic alcohol **8** as the major product with α-preference (run 2), accompanied with the enone **10** and only a trace amount of the epoxide **9**. This trend is similar that in the reaction of **1** (run 1) that we reported before. Run 3 shows the oxygenation of **6b**, affording **11** as the major product with β-preference, together with the enone **13** and a trace of **12**. The reaction of **7b**, which has a structurally different alkene, gave only small amounts of the alcohol **14** and ketone **16**, and most of the substrate was recovered unchanged (run 4). Thus, oxygenation of **7b** did not proceed effectively in this condition.

These results indicate that the nature of the AB ring is important for the 7α-hydroxylation of steroids, that is, the bridgehead double bond is essential for allylic hydroxylation. A C5–C6 alkene moiety meets the structural requirement, but a non-bridgehead double bond such as the C8–C9 alkene of **7b** does not.

We also investigated chemical oxygenation using the $Fe^{III}(PA)_3/H_2O_2/CH_3CN$ system[18—20] for comparison with the electrochemical reaction, and the results are summarized in Table 2. In runs 5 and 6, the allylic hydroxylated products were formed with α-preference, but with significant amounts of ketones. In these reactions, the epoxides **9** and **12** were also obtained as α/β mixtures. Run 7 shows that this chemical method gave mainly the ketone **16** from **7b**, accompanied with the epoxide **15**, and was unsuitable for allylic hydroxylation.

The α/β ratio of hydroxylated products was almost constant in runs 2, 3, 5 and 6. This trend suggests that the stereoselectivity depends upon steric factors of the substrate, as we reported before,[21] *e.g.*, steric hindrance of the 10-methyl group, or the conformation of the B-ring. This view is supported by the fact that the stereoselectivity in hydroxylation is slightly less than, but in a similar direction to, that in the hydroxylation of cholesteryl acetate **1**. In addition, the 7α-preference is not related to the neighboring effect of the benzoxy group.

The stereochemistry of **8α/β** was confirmed by the ^{1}H-NMR peak of olefinic C6-H. The coupling constant of C6-H of **8α** was 4.4 Hz, and C6-H of **8β** shows a broad singlet peak. This can be understood from the fact that, although the dihedral angle of H-C6–C7-βH of **8α** is close to 20°, H-C6–C7-αH of **8β** is nearly 90° and this coupling cannot be observed. The epoxides **9α/β** were determined from the C6-H peak. The C6-βH peak of **9α** shows a doublet of 5.0 Hz, and C6-αH of **9β** shows a triplet of 2.6 Hz. Although the dihedral angles of αH-C6–C7-H_2 of **9β** are both about 50°—60°, βH-C6–C7-αH of **9α** is almost 90° and only βH-C6–C7-βH coupling can be observed (5.0 Hz). The stereochemistries of **11**, **12**, **14** and **15** were determined similarly.

Table 1. The Yields of Electrochemical Oxygenation Reactions

Run	Substrate	Product (%)[a]			
		Allylic-OH	Epoxides	Allylic ketone	Recovery
1[b]	**1**	**2**: 21% ($\alpha:\beta$=93:7)	**3**: trace	**4**: 11%	**1**: 26%
2	**5b**	**8**: 23% ($\alpha:\beta$=87:13)	**9**: trace	**10**: 7%	**5b**: 26%
3	**6b**	**11**: 20% ($\alpha:\beta$=84:16)	**12**: trace	**13**: 7%	**6b**: 36%
4	**7b**	**14**: 6% ($\alpha:\beta$=75:25)	**15**: trace	**16**: 3%	**7b**: 64%

a) The yields are isolated yields as α/β mixture, and the ratios of α/β isomers were calculated from the integration values of the methine proton signals in ^{1}H-NMR measurement. *b*) Our previously reported data (ref. 21).

Table 2. The Chemical Oxygenation Reactions

Run	Substrate	Product (%)[a]			
		Allylic-OH	Epoxides	Allylic ketone	Recovery
5	**5b**	**8**: 11% ($\alpha:\beta$=84:16)	**9**: 10% ($\alpha:\beta$=70:30)	**10**: 25%	**5b**: 16%
6	**6b**	**11**: 15% ($\alpha:\beta$=83:17)	**12**: 9% ($\alpha:\beta$=69:31)	**13**: 28%	**6b**: 9%
7	**7b**	**14**: trace	**15**: 13% ($\alpha:\beta$=61:39)	**16**: 30%	**7b**: 5%

a) The yields are isolated yields as α/β mixture, and the ratios of α/β isomers were calculated from the integration values of the methine proton signals in ^{1}H-NMR measurement.

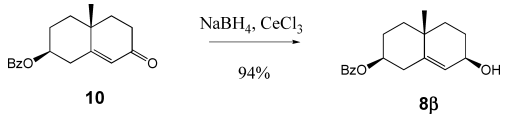

Chart 3. Stereoselective Reduction of **10**

These stereochemistries are also supported by the following results. Only the β-OH product **8**$\boldsymbol{\beta}$ was obtained when the ketone **10** was reduced with $NaBH_4$ in the presence of $CeCl_3$[28] in 94% yield (Chart 3). The similar reduction of **13** and **16** gave **11**$\boldsymbol{\beta}$ (74%) and **14**$\boldsymbol{\beta}$ (70%), respectively, as a single isomer. The epoxidation of **7b** with *m*CPBA (*m*-chloroperbenzoic acid) gave only **15**$\boldsymbol{\alpha}$ in accordance with the reported selectivity.[29,30]

Conclusion

We examined the regio- and stereoselectivity of the electrochemical oxygenation of octahydronaphthalene derivatives. The electrochemical oxygenation method using $Fe^{III}(PA)_3/O_2$/electrolysis/CH_3CN is expected to be a useful tool for α-selective allylic hydroxylation of fused cyclic olefins, such as the AB ring of cholesterol, while leaving a cyclic alkene moiety at a non-fused position intact.

Experimental

All melting points are uncorrected. Electrolyses were performed with Yanaco VE-9. Infrared (IR) spectra were recorded with a Shimadzu FTIR-8200A spectrometer, and ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL JNM-AL300 spectrometers, with tetramethylsilane as an internal standard ($CDCl_3$ solution). Chemical shifts are recorded in ppm, and coupling constants (*J*) are in Hz. In the assignment of the peaks, the numbering of carbons follows that of cholesterol. Mass spectra were recorded on JEOL JMS-D300 and HX110 spectrometers. Elemental analyses were performed on an Amco Flash EA 1112 instrument. Merck silica gel 60 (1.09385) and Merck silica gel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively. Preparative HPLC was carried out with a JASCO HPLC system (pump, JASCO 880PU; UV detector, JASCO UV-970) using a silica gel (Wakosil, 5C4-200, 20 mm×250 mm) column.

Preparation of Substrates The precursors (±)-**5a**,[25] (±)-**6a**[26] and (±)-**7a**[27] were benzoylated according to the following general procedure. To a solution of 1.8 mmol of alcohol, 7.0 mmol of benzoic anhydride and 0.25 mmol of 4-dimethylaminopyridine were added, and the resulting mixture was stirred at room temperature for 15 h, then poured into 10% hydrochloric acid, and extracted with ether. The combined organic layer was washed with sat. sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed with a rotary evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 20), affording the benzoylated compound.

2β-Benzoxy-4aβ-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**5b**): Colorless oil (65% from **5a**) ^{1}H-NMR δ: 8.05 (2H, dd, *J*=7.0, 1.5, *o*-), 7.55 (1H, tt, *J*=7.3, 2.0, *p*-), 7.43 (2H, t, *J*=7.3, *m*-), 5.46 (1H, m, C6-H), 4.87 (1H, tt, *J*=5.5, 5.5, C3-H), 2.43 (2H, m), 1.14 (3H, s, CH_3). ^{13}C-NMR δ: 165.99, 139.25, 132.71, 130.82, 129.53, 128.26, 123.22, 74.77, 39.09, 38.95, 38.05, 33.86, 27.83, 25.78, 24.16, 18.95. IR (KBr) cm^{-1}: 1717, 1273. LR-MS (EI) *m/z*: 270 (M^+), HR-MS (EI) Calcd for $C_{18}H_{22}O_2$: 270.1620; Found: 270.1597.

1β-Benzoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (**6b**): Colorless oil (64% from **6a**) ^{1}H-NMR δ: 8.05 (2H, dd, *J*=7.0, 1.5, *o*-), 7.55 (1H, tt, *J*=7.3, 2.0, *p*-), 7.44 (2H, t, *J*=7.3, *m*-), 5.49 (1H, m, C6-H), 4.82 (1H, dd, *J*=11.4, 4.6), 1.25 (3H, s, CH_3). ^{13}C-NMR δ: 166.08, 140.98, 132.73, 130.84, 129.52, 128.31, 122.74, 81.17, 39.61, 35.75, 31.47, 27.55, 25.66, 24.78, 18.88, 18.57. IR (KBr) cm^{-1}: 1717, 1273. LR-MS (EI) *m/z*: 270 (M^+), HR-MS (EI) Calcd for $C_{18}H_{22}O_2$: 270.1620; Found: 270.1612.

2β-Benzoxy-4aβ-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (**7b**): Colorless plates (recryst from H_2O) (84% from **7a**) mp: 32.0—32.5 °C ^{1}H-NMR δ: 8.04 (2H, dd, *J*=7.0, 1.5, *o*-), 7.53 (1H, tt, *J*=7.3, 2.0, *p*-), 7.42 (2H, t, *J*=7.3, *m*-), 5.50 (2H, m, C8-H, C9-H), 5.00 (1H, m, C3-H), 0.97 (3H, s, CH_3). ^{13}C-NMR δ: 166.07, 138.09, 132.68, 130.85, 129.52, 128.24, 124.57, 74.27, 40.42, 36.70, 34.03, 33.67, 27.30, 25.78, 25.03, 18.88. IR (KBr) cm^{-1}: 1713, 1279. LR-MS (EI) *m/z*: 270 (M^+), HR-MS (EI) Calcd for $C_{18}H_{22}O_2$: 270.1620; Found: 270.1596. *Anal.* Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.97; H, 8.39.

Iron(III) Picolinate Complexes Iron(III) perchlorate was a commercial product, used without further purification. The iron picolinate complex was prepared according to the method we reported before, and used in hydrated form.

General Procedure for Electrochemical Method Substrate **5b** (75 mg, 0.28 mmol) and 24 mg of $Fe^{III}(PA)_3H_2O$ (0.05 mmol) were dissolved in a 0.1 M solution of tetra-*n*-butylammonium tetrafluoroborate in 40 ml of acetonitrile. In an H-shaped glass cell equipped with platinum mesh electrodes (cathode and anode), this reaction mixture was electrolyzed in a constant-potential manner at −0.10 V *vs.* the Ag/AgCl reference electrode with O_2 gas bubbling and magnetic stirring. After 1 h, the resulting mixture was poured into ice-water, and extracted with ether. The combined organic layer was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, and filtered. The solvent was removed with an evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 10 then 1 : 4), to afford **10**, recovered **5b**, a mixture of **8**$\boldsymbol{\alpha}$ and **8**$\boldsymbol{\beta}$, and a trace amount of **9**, and the yields were recorded. The product ratio of **8**$\boldsymbol{\alpha}$/**8**$\boldsymbol{\beta}$ were measured in terms of the integration ratio of the methine proton peak. Further separation of **8**$\boldsymbol{\alpha}$/**8**$\boldsymbol{\beta}$ was performed with HPLC (ethyl acetate : hexane = 1 : 20).

General Procedure for Chemical Method Substrate **5b** (75 mg, 0.28 mmol) and $Fe^{III}(PA)_3H_2O$ 24 mg (0.05 mmol) were dissolved in 20 ml of acetonitrile, and 0.05 ml of 35% hydrogen peroxide solution was added four times at 30-min intervals. The resulting mixture was stirred at ambient temperature for 3 h, then poured into ice-water, and extracted with ether. The combined organic layer was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, and filtered. The solvent was removed with a rotary evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 10 then 1 : 4), to afford **10**, recovered **5b**, a mixture of **8**$\boldsymbol{\alpha}$ and **8**$\boldsymbol{\beta}$, and a mixture of **9**$\boldsymbol{\alpha}$ and **9**$\boldsymbol{\beta}$, and the yields were recorded. The product ratio of **8**$\boldsymbol{\alpha}$/**8**$\boldsymbol{\beta}$ and **9**$\boldsymbol{\alpha}$/**9**$\boldsymbol{\beta}$ was measured in terms of the integration ratio of the methine proton peak. Further separation of **8**$\boldsymbol{\alpha}$/**8**$\boldsymbol{\beta}$ was performed with HPLC (ethyl acetate : hexane = 1 : 20), and **9**$\boldsymbol{\alpha}$/**9**$\boldsymbol{\beta}$ were separated with flash-chromatography (dichloromethane : hexane = 2 : 1).

Characteristic ^{1}H-NMR signals and other spectral data are as follows:

7β-Benzoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2α-ol (**8**$\boldsymbol{\alpha}$): ^{1}H-NMR δ: 8.05 (2H, dd, *J*=8.4, 1.5, *o*-), 7.56 (1H, tt, *J*=7.3, 2.2, *p*-), 7.44 (2H, t, *J*=7.2, *m*-), 5.60 (1H, br d, *J*=4.4, C6-H), 4.92 (1H, tt, *J*=11.4, 5.1, C3-H), 4.12 (1H, m, C7-H), 2.53 (1H, ddd, *J*=12.9, 5.1, 2.0), 2.42 (1H, tt, *J*=11.2, 1.8), 1.12 (3H, s, CH_3). ^{13}C-NMR δ: 165.88, 144.32, 132.82, 130.60, 129.54, 128.29, 124.88, 74.08, 64.46, 38.31, 37.71, 34.30, 33.53, 27.88, 27.60, 22.84. IR (KBr) cm^{-1}: 3504, 1715, 1275. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1667.

7β-Benzoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2β-ol (**8**$\boldsymbol{\beta}$): ^{1}H-NMR δ: 8.05 (2H, dd, *J*=8.4, 1.5, *o*-), 7.56 (1H, tt, *J*=7.3, 2.2, *p*-), 7.44 2H, t, *J*=7.7, *m*-), 5.46 (1H, br s, C6-H), 4.89 (1H, tt, *J*=11.4, 5.0, C3-H), 4.24 (1H, ddd, *J*=11.2, 5.9, 2.2, C7-H), 2.50 (1H, ddd, *J*=13.0, 5.5, 2.2), 2.41 (1H, tt, *J*=11.2, 2.0), 1.19 (3H, s, CH_3). ^{13}C-NMR δ: 165.91, 142.18, 132,82, 130.56, 129.52, 128.27, 126.96, 74.38, 67.77, 38.85, 37.63, 36.62, 34.13, 29.01, 27.74, 23.61. IR (KBr) cm^{-1}: 3403, 1717, 1275. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1650.

7β-Benzoxy-1,8aα-epoxy-4aβ-methyldecahydronaphthalene (**9**$\boldsymbol{\alpha}$): ^{1}H-NMR δ: 8.04 (2H, d, *J*=7.9, *o*-), 7.56 (1H, tt, *J*=7.3, 2.2, *p*-), 7.44 (2H, t, *J*=7.9, *m*-), 5.02 (1H, m, C3-H), 3.06 (1H, d, *J*=5.0, C6-H), 2.30 (1H, t, *J*=12.1), 1.14 (3H, s, CH_3). ^{13}C-NMR δ: 165.92, 132.92, 130.40, 129.57, 128.31, 72.32, 61.93, 61.32, 37.23, 34.07, 32.59, 31.90, 27.24, 24.09, 22.93, 16.19. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1635.

7β-Benzoxy-1,8aβ-epoxy-4aβ-methyldecahydronaphthalene (**9**$\boldsymbol{\beta}$): ^{1}H-NMR δ: 8.02 (2H, dd, *J*=8.4, 1.5, *o*-), 7.54 (1H, tt, *J*=7.3, 2.2, *p*-), 7.42 (2H, t, *J*=7.3, *m*-), 5.24 (1H, tt, *J*=11.6, 5.0, C3-H), 2.96 (1H, t, *J*=2.6, C6-H), 2.25 (1H, dd, *J*=12.7, 11.6), 1.18 (3H, s, CH_3). ^{13}C-NMR δ: 165.72, 132.75, 130.67, 129.52, 128.26, 72.20, 64.22, 59.34, 35.71, 34.89, 33.17, 32.47, 27.30, 21.77, 20.53, 15.63. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1632.

7β-Benzoxy-4aβ-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one

(**10**): Colorless prisms (recryst from ethyl acetate–hexane) mp: 115.5—116.5 °C ^{1}H-NMR δ 8.05 (2H, dd, J=7.0, 1.5, *o*-), 7.58 (1H, tt, J=7.3, 2.0, *m*-), 5.83 (1H, d, J=2.0, C6-H), 5.02 (1H, tt, J=11.4, 4.8, C3-H), 2.75 (1H, ddd, J=14.1, 5.1, 2.2), 2.40 (1H, dt, J=17.4, 3.7), 1.53 (1H, dt, J=3.85, 13.8), 1.33 (3H, s, CH_3). ^{13}C-NMR δ: 199.04, 165.75, 165.56, 133.06, 130.18, 129.57, 128.36, 126.41, 72.82, 38.19, 37.94, 37.31, 35.14, 33.87, 27.37, 21.96. IR (KBr) cm^{-1}: 1720, 1672, 1275. LR-MS (EI) *m/z*: 284 (M^+), HR-MS (EI) Calcd for $C_{18}H_{20}O_3$: 284.1412; Found: 284.1426. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.98; H, 7.17.

5β-Benzoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2α-ol (**11α**): ^{1}H-NMR δ: 8.04 (2H, dd, J=8.4, 1.5, *o*-), 7.56 (1H, tt, J=7.3, 2.2, *p*-), 7.44 (2H, t, J=7.3, *m*-), 5.61 (1H, dd, J=4.2, 1.7, C6-H), 4.86 (1H, dd, J=11.6, 4.6, C1-H), 4.12 (1H, m, C7-H), 1.23 (3H, s, CH_3). ^{13}C-NMR δ: 165.94, 145.48, 132.86, 130.62, 129.54, 128.35, 124.70, 80.09, 64.70, 39.86, 31.23, 30.30, 27.70, 27.30, 24.25, 18.00. IR (KBr) cm^{-1}: 3464, 1717, 1275. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1637.

5β-Benzoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2β-ol (**11β**): ^{1}H-NMR δ: 8.03 (2H, dd, J=8.4, 1.5, *o*-), 7.56 (tt, J=7.3, 2.2, *p*-), 7.44 (2H, t, J=7.3, *m*-), 5.48 (1H, br s, C6-H), 4.77 (1H, dd, J=11.6, 4.4, C1-H), 4.20 (1H, m, C7-H), 1.30 (3H, s, CH_3). ^{13}C-NMR δ: 165.99, 143.72, 132.89, 130.57, 129.52, 128.37, 126.48, 80.79, 67.41, 39.89, 33.25, 31.14, 28.51, 27.43, 24.34, 18.35. IR (KBr) cm^{-1}: 3412, 1717, 1275. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1668.

5β-Benzoxy-1,8aα-epoxy-4aβ-methyldecahydronaphthalene (**12α**): ^{1}H-NMR δ: 8.04 (2H, dd, J=1.5, 8.6, *o*-), 7.57 (1H, tt, J=7.5, 1.5, *p*-), 7.45 (2H, t, J=7.7, *m*-), 5.28 (1H, dd, J=11.4, 4.8, C1-H), 2.99 (1H, d, J=5.0, C6-H), 2.13 (1H, dt, J=4.4, 13.6), 1.26 (3H, s, CH_3), 1.05 (1H, br d, J=13.2). ^{13}C-NMR δ: 165.89, 132.97, 130.42, 129.59, 128.40, 73.64, 63.53, 61.44, 38.85, 30.69, 28.88, 26.59, 23.73, 20.82, 18.17, 15.69. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1643.

5β-Benzoxy-1,8aβ-epoxy-4aβ-methyldecahydronaphthalene (**12β**): ^{1}H-NMR δ: 8.02 (2H, br d, J=7.0, *o*-), 7.55 (1H, tt, J=7.5, 2.0, *p*-), 7.43 (2H, t, J=7.3, *m*-), 5.09 (1H, dd, J=11.0, 5.0, C1-H), 2.97 (1H, t, J=2.0, C6-H), 1.31 (3H, s, CH_3), 0.98 (1H, br d, J=11.2). ^{13}C-NMR 165.87, 132.76, 130.74, 129.52, 128.31, 79.00, 64.93, 59.04, 38.22, 29.99, 29.22, 26.93, 22.07, 20.48, 16.22, 15.25. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1639.

5β-Benzoxy-4aβ-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (**13**): The spectral data are identical to those reported.[31] ^{1}H-NMR δ: 8.05 (2H, dd, J=8.4, 1.5, *o*-), 7.59 (1H, tt, J=7.3, 2.2, *p*-), 7.46 (2H, t, J=7.3, *m*-), 5.86 (1H, d, J=1.8, C6-H), 4.92 (1H, dd, J=11.6, 4.4, C1-H), 1.44 (3H, s, CH_3). ^{13}C-NMR δ: 198.90, 166.60, 165.74, 133.17, 130.14, 129.56, 128.47, 125.90, 79.75, 40.74, 34.13, 33.48, 31.80, 26.95, 22.94, 16.92. IR (KBr) cm^{-1}: 1672, 1275, 1717. LR-MS (EI) *m/z*: 284 (M^+), HR-MS (EI) Calcd for $C_{18}H_{20}O_3$: 284.1412; Found: 284.1400.

7β-Benzoxy-4aβ-methyl-1,2,4a,5,6,7,8,8aα-octahydronaphthalen-2α-ol (**14α**): ^{1}H-NMR δ: 8.04 (2H, dd, J=8.4, 1.5, *o*-), 7.55 (1H, tt, J=7.3, 1.5, *p*-), 7.43 (2H, t, J=7.3, *m*-), 5.76 (1H, d, J=9.9, C9-H), 5.66 (1H, ddd, J=9.7, 4.2, 1.3, C8-H), 5.03 (1H, tt, J=11.2, 5.3, C3-H), 4.17 (1H, t, J=4.2, C7-H), 0.95 (3H, s, CH_3). ^{13}C-NMR δ: 166.01, 142.41, 132.76, 130.74, 129.53, 128.26, 125.76, 73.94, 64.33, 36.05, 35.17, 34.65, 34.61, 33.16, 27.22, 17.26. IR (KBr) cm^{-1}: 3410, 1717, 1277. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1661.

7β-Benzoxy-4aβ-methyl-1,2,4a,5,6,7,8,8aα-octahydronaphthalen-2α-ol (**14β**): ^{1}H-NMR δ: 8.04 (2H, dd, J=8.4, 1.5, *o*-), 7.55 (1H, tt, J=7.5, 2.2, *p*-), 7.43 (2H, t, J=7.9, *m*-), 5.61 (1H, dd, J=10.1, 1.5, C8-H or C9-H), 5.50 (1H, br d, J=10.1, C9-H or C8-H), 4.98 (1H, tt, J=10.8, 5.3, C3-H), 4.38 (1H, br d, J=8.8, C7-H), 1.05 (3H, s, CH_3). ^{13}C-NMR δ: 166.03, 140.06, 132.77, 130.61, 129.49, 128.25, 128.21, 73.72, 68.57, 39.28, 36.26, 35.31, 34.60, 33.21, 27.08, 18.75. IR (KBr) cm^{-1}: 3438, 1717, 1277. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1632.

6β-Benzoxy-1,2α-epoxy-8aβ-methyl-4aα-decahydronaphthalene (**15α**): ^{1}H-NMR δ: 8.03 (2H, dd, J=8.6, 1.5, *o*-), 7.54 (1H, tt, J=7.3, 1.5, *p*-), 7.42 (2H, t, J=7.3, *m*-), 4.95 (1H, tt, J=10.8, 5.1, C3-H), 3.13 (1H, t, J=4.0, C8-H or C9-H), 2.82 (1H, d, J=4.0, C9-H or C8-H), 1.04 (3H, s, CH_3). ^{13}C-NMR δ: 165.93, 132.71, 130.75, 129.49, 128.24, 73.56, 61.78, 52.45, 34.29, 33.38, 33.15, 33.12, 27.06, 23.13, 22.22, 15.10. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1658.

6β-Benzoxy-1,2β-epoxy-8aβ-methyl-4aα-decahydronaphthalene (**15β**): ^{1}H-NMR δ: 8.03 (2H, dd, J=8.6, 1.5, *o*-), 7.55 (1H, tt, J=7.3, 2.0, *p*-), 7.43 (2H, t, J=7.9, *m*-), 4.98 (1H, tt, J=11.2, 5.5, C3-H), 3.20 (1H, br s, C8-H or C9-H), 2.81 (1H, d, J=3.7, C9-H or C8-H), 2.15 (1H, dd, J=15.0, 4.8), 1.05 (3H, s, CH_3). ^{13}C-NMR δ: 166.07, 132.80, 130.65, 129.52, 128.27, 73.78, 61.02, 53.89, 41.35, 36.37, 32.69, 32.52, 27.13, 26.62, 22.29, 13.73. LR-MS (FAB) *m/z*: 287 ($[M+H]^+$), HR-MS (FAB) Calcd for $C_{18}H_{23}O_3$ ($[M+H]^+$): 287.1647; Found: 287.1636.

7β-Benzoxy-4aβ-methyl-4a,5,6,7,8,8aα-hexahydro-1*H*-naphthalen-2-one (**16**): ^{1}H-NMR δ: 8.04 (2H, dd, J=8.6, 1.5, *o*-), 7.56 (1H, tt, J=7.3, 2.2, *p*-), 7.44 (2H, t, J=7.3, *m*-), 6.81 (1H, d, J=9.9, C3-H), 5.88 (1H, d, J=9.9, C4-H), 5.01 (1H, tt, J=11.2, 5.1, C7-H), 1.17 (3H, s, CH_3). ^{13}C-NMR δ: 199.17, 165.91, 160.06, 132.91, 130.39, 129.51, 128.30, 127.29, 72.70, 40.51, 40.14, 35.46, 35.41, 32.76, 26.98, 16.44. IR (KBr) cm^{-1}: 1717, 1672, 1281. LR-MS (EI) *m/z*: 284 (M^+), HR-MS (EI) Calcd for $C_{18}H_{20}O_3$: 284.1412; Found: 284.1390.

Reduction of 10 to 8β This stereoselective reduction was carried out according to the well-known procedure for steroids.[28] To a solution of 111 mg of **10** (0.39 mmol) in 4 ml of dichloromethane was added a solution of 282 mg of cerium(III) chloride heptahydrate (0.76 mmol) in 1.5 ml of methanol. The resulting solution was stirred at −78 °C, and 32 mg of sodium borohydride (0.85 mmol) was added. Stirring was continued for 1 h, then the mixture was poured into 5% hydrochloric acid, and extracted with ether. The combined organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed with a rotary evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 4 then 1 : 1) to afford 105 mg of **8β** (94%). The stereoselective reduction of **13** and **16** were performed with similar procedure.

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