

Syntheses of Anisomycin Derivatives

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Anisomycin derivatives have been synthesized via syn-amidoalkylation followed by installation of *p*-methoxyphenyl group and subsequent transformation.

Introduction

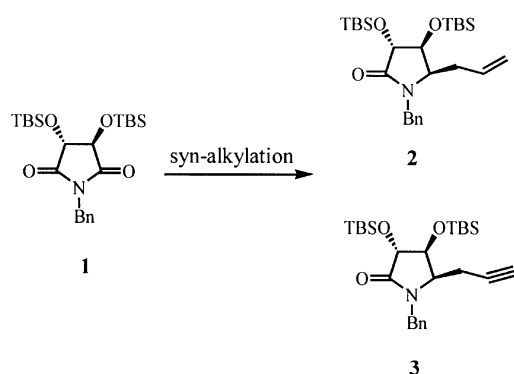
Anisomycin is a fermentation product of various *Streptomyces*¹ and an antibiotic that possesses marked activities against pathogenic protozoa and fungi, and has been used successfully in the clinical treatment of amebic dysentery and trichomonas vaginitis.² It has been verified to block ribosomal peptide synthesis.³



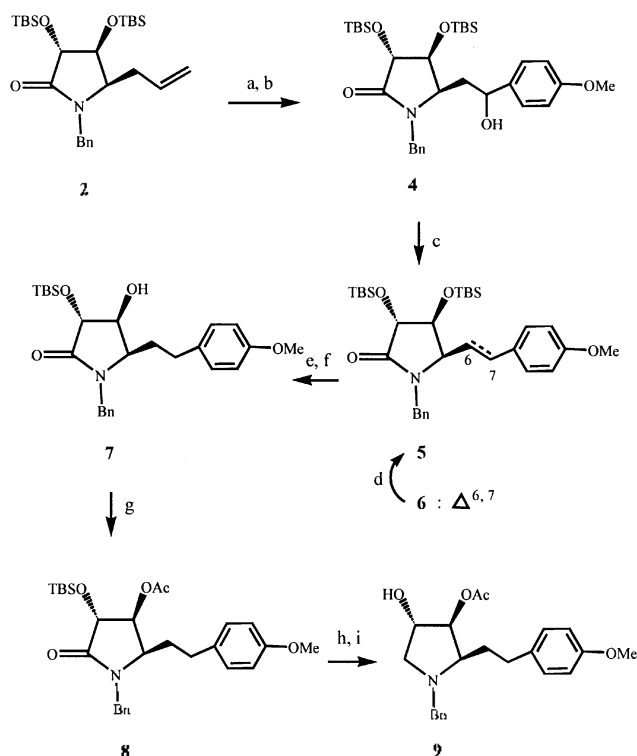
The structure of anisomycin has been determined by X-ray investigation⁴ and the absolute configuration was confirmed by chemical correlation.⁵ Anisomycin has attracted considerable synthetic interest, and several synthetic studies, derivative syntheses as well as total syntheses, have been reported.⁶ Especially, the synthesis of its analogues has revealed the structure-activity relationship of the synthetic antibiotics.⁷ As we are interested in the effect of chain extension of the *p*-methoxybenzyl group in the molecule, we have developed a new synthetic approach to the anisomycin related compounds. In this approach, stereoselective cis-amidoalkylation has been employed to requisite intermediates.⁸ Here, we disclose the details of the syntheses of the derivatives.

Results and Discussion

A homoanisomycin derivative, *N*-benzylhomo(-)-anisomycin, was our first synthetic target.⁹ The allylic amide **2** was suitable for manipulation to the compound. In order to



make one carbon extended side chain, the amide **2** was subjected to ozonolysis and the reductive work-up using methyl sulfide. Without purification, the corresponding aldehyde was treated with (*p*-methoxyphenyl)magnesium bromide¹⁰ in THF to yield an epimeric mixture of benzylic alcohols in 59% overall yield. To remove the alcohol group of **4**, various reductive conditions have been applied. The treatment of **4** with triethylsilane in the presence of trifluoroacetic acid in THF proved to be the best condition, providing **5** in 70% yield and β -elimination product **6** in less than 10% yield. Practically the crude mixture was exposed to hydrogen in the presence of Pd-catalyst to converge **6** to **5**, and then purified. The lactam ring functional groups of **5** holding the desired side group then needs transformation to the desired structure. As the stereochemistry of **5** was positioned as required, acetate functionality at the C-3 position and



Scheme 2. Reagents and conditions: (a) i. O₃, CH₂Cl₂-MeOH ii. Methyl sulfide (b) (*p*-Methoxyphenyl)magnesium bromide, THF (c) Et₃SiH, CH₂Cl₂, TFA (d) Pd/5%, H₂ (e) TBAF, THF (f) TBSCl, imidazole, DMF (g) Ac₂O, pyridine (h) TBAF, THF (i) BH₃-DMS, THF, rt.

could be installed by using steric hindrance resulting from the side chain and pseudo convex face.

Deprotection of TBS groups of **5** by tetrabutylammonium fluoride (TBAF) provided a diol, and the sterically less hindered α -hydroxy group of the diol was specifically silylated when treated with 1.2 equiv. of *tert*-butyldimethylsilyl chloride in DMF at 0 °C. Acetylation of the 3-hydroxyl group with acetic anhydride in pyridine yielded the acetate **7** in overall yield of 52%. Finally removal of the protecting silyl group with TBAF was followed by reduction of the amide group with borane-demethyl sulfide complex to afford *N*-benzylhomo(-)-anisomycin **3** with 34% yield in 2 steps.

For the preparation of other related compounds which have two more carbons extended in the side chain, intermediate **3** was selected as a proper intermediate. The terminal acetylene functional group would be suitable for the attachment of various aromatic functionalities. In order to test the coupling reaction of the intermediate **3** with aromatic halides, various reaction conditions have been tried. Two conditions seem to be worth mentioning. The conventional condition of the terminal acetylene coupling reaction, using palladium reagent (PdCl₂(Ph₃P)₂, CuI, Et₃N),¹¹ suffered from the formation of inseparable self-dimerization product of the acetylene **3** in 10 to 20% yield. This side reaction could be suppressed by use of highly purified CuI. Impurity from CuI appeared to induce the self-dimerization. Interestingly, while this work was being carried, it was reported that the addition of some trace of I₂ in the condition provided excellent yields of self-coupling product diynes.¹² Alternatively, use of CuI and PPh₃ reagents in DMF in the presence of K₂CO₃ yielded the desired products in affordable yields with no trace of the by-products, though heating at 100 °C–120 °C for 16 hr was required for the coupling (Table 1).¹³

Among those coupled derivatives **10**, compound **10a** was representatively transformed to an anisomycin analogue **15**. Compound **10a** was reduced to **11** using palladium on char-

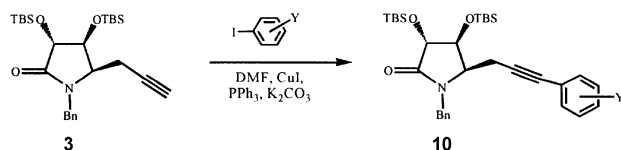


Table 1. Coupling reaction of **3** with aromatic halides

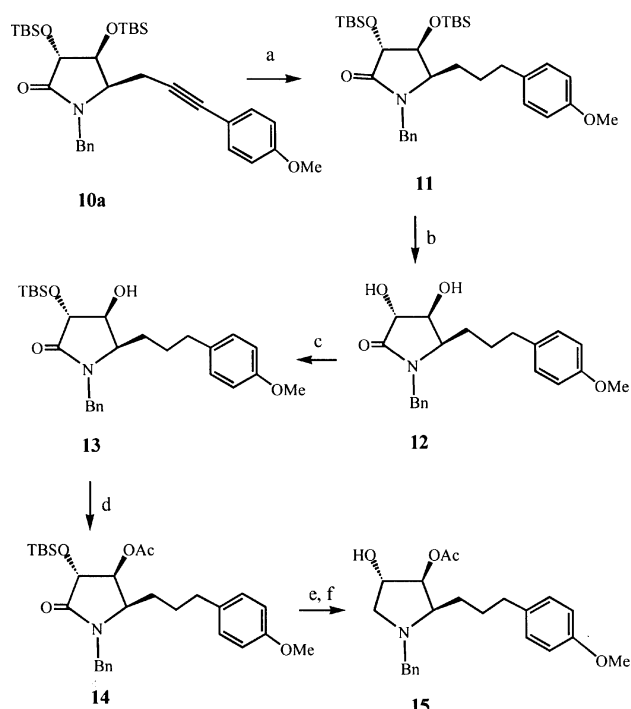
| Entry | Substrate | Yield of 10 (%) |
|-------|-----------|------------------------|
| a | | 76 |
| b | | 66 |
| c | | 70 |
| d | | 70 |

col (5%) under atmospheric H₂ pressure in 63% yield. The same sequence of transformations as that for the *homo*-anisomycin derivative **3** was applied. TBAF treatment of compound **11** in THF provided diol **12** in 82% yield. Selective acetylation of 3- β -hydroxyl group of the diol was achieved by treatment of **12** with 1.2 equiv. of *tert*-butyldimethylsilyl chloride in CH₂Cl₂ to provide **13** in 38% yield, and acetylation with acetic anhydride in pyridine yielded the desired product **14** in 68% yield. The final transformation to **15** involved deprotection of TBS group with TBAF and reduction of the amide group in 28% yield. Obviously, the more closely related derivatives would be the debenzylated compounds of **9** and **15**. However, several attempts for the deprotection resulted in the failure of obtaining the desired products. Reductive conditions mainly decomposed the materials.

In summary, compounds related with anisomycin, *N*-benzylhomo(-)-anisomycin and its analogue have been synthesized. *Syn*-amidoalkylation afforded the key intermediates for the syntheses. Coupling reaction of the acetylenic compound with aromatic halides have suggested that various aromatic functionality can be attached and length of the side chain can be also extended. The study of biological activity and structural relationship will be pursued in future.

Experimental Section

General. All commercial chemicals were used as obtained without further purification, and all solvents were carefully dried and distilled by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck).



Scheme 3. Reagents and conditions: (a) Pd/5%, H₂, MeOH (b) TBAF, THF (c) TBSCl, imidazole, CH₂Cl₂ (d) Ac₂O, pyridine (e) TBAF, THF (f) BH₃-DMS, THF.

230–400 mesh) with the flash technique. Thin-layer chromatography was performed on E. Merck 60F-254 precoated silica plates (0.25 mm layer thickness). NMR spectra were determined on a Bucker ARX 300 spectrometer. Chemical shifts are reported in δ ppm relative to $(\text{CH}_3)_4\text{Si}$ for ^1H and ^{13}C NMR. Coupling constant J are reported in Hz. Infrared spectra (cm^{-1}) were obtained on a Nicolet 710 FT-IR spectrometer. Mass spectra were obtained from HIT, Taejon, Korea.

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[2'-hydroxy-2'-(*p*-methoxyphenyl)ethyl]-1-benzyl-2-pyrrolidinone (4). To a solution of **2** (500 mg, 1.1 mmol) in methanol:methylene chloride solution (10 mL : 1 mL) was bubbled O_3 stream at -78°C until the blue color persisted. To the reaction mixture was added 1 ml of dimethyl sulfide at -78°C , and the mixture was warmed to room temperature. The solvent was evaporated on rotary evaporator to yield a crude aldehyde. The aldehyde was dissolved in dry THF (5 ml) and *p*-methoxyphenylmagnesium bromide which was prepared by treatment of *p*-methoxyphenyl bromide (2.3 mmol) with an excess of Mg in dry ether was added dropwise to the solution and the mixture was warmed to room temperature. The mixture was diluted with 10 mL of EtOAc, and the organic layer was washed with sat'd NH_4Cl solution twice and brine once, and dried over MgSO_4 . After filtration the crude compounds were purified by silica-gel column chromatography to afford an epimeric mixture of compound **4** as an oil (376 mg, 59%); an epimer, ^1H NMR (300 MHz, CDCl_3) δ 7.01–7.20 (5H, m), 6.81 (2H, d, $J=9.0$ Hz), 6.72 (2H, d, $J=9.0$ Hz), 4.71 (1H, d, $J=9.0$ Hz), 4.29 (1H, m), 4.09 (1H, m), 3.91 (1H, d, $J=15.0$ Hz), 3.65 (3H, s), 3.28 (1H, m), 2.09–2.30 (2H, m), 1.69 (1H, m), 0.81, 0.92 (9H \times 2, s), -0.21, -0.11, 0.00, 0.11 (3H \times 4, s); IR (CHCl_3) 3430, 3054, 2305, 1703, 1512, 1422, 1265 cm^{-1} ; MS (FAB, glycerol) 586 (M^+).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[2'-(*p*-methoxyphenyl)ethyl]-1-benzyl-2-pyrrolidinone (5). To a solution of compound **4** (970 mg, 1.7 mmol) in methylene chloride were added trifluoroacetic acid (0.75 mL) and triethylsilane (1.5 mL) at 0°C . The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of water and diluted with methylene chloride. The organic layer was washed with sat'd NaHCO_3 solution, and dried over MgSO_4 . After concentration the mixture was purified by silica-gel column to afford compound **5** as an oil (660 mg, 70%); ^1H NMR (300 MHz, CDCl_3) δ 7.09–7.20 (5H, m), 6.78 (2H, d, $J=9.0$ Hz), 6.59 (2H, d, $J=9.0$ Hz), 4.70 (1H, d, $J=15.0$ Hz), 4.09 (1H, m), 4.01 (1H, m), 3.88 (1H, d, $J=15.0$ Hz), 3.57 (3H, s), 3.29 (1H, m), 2.18–2.40 (2H, m), 1.48–1.70 (2H, m), 0.79, 0.90 (9H \times 2, s), 0.20, 0.09, 0.01, 0.12 (3H \times 4, s); IR (CHCl_3) 2953, 1685, 1511, 1248 cm^{-1} ; MS (FAB, glycerol) 570 (M^+).

(3R,4R,5R)-3-*tert*-Butyldimethylsilyloxy-4-hydroxy-5-[2'-(*p*-methoxyphenyl)ethyl]-1-benzyl-2-pyrrolidinone (7). Compound **5** (568 mg, 1.0 mmol) was dissolved in THF (5 mL), and TBAF (1 M in THF, 2.4 mL) was added. The reaction mixture was stirred for 4 h at room temperature. The organic layer diluted with 10 mL of EtOAc was washed with sat'd NH_4Cl solution three times and brine once, dried

over MgSO_4 . The mixture was filtered and the filtrate was concentrated to afford a crude diol (275 mg, 85%). The diol was dissolved in 4 mL of dry DMF, and to this solution were added TBSCl (121 mg, 0.80 mmol) and imidazole (109 mg, 1.61 mmol). The resulting solution was stirred at room temperature overnight under N_2 , and water was added. The mixture was extracted with EtOAc three times, and the organic layer was washed with sat'd NH_4Cl solution twice and brine once. After drying over MgSO_4 and filtration, the filtrate was concentrated under vacuum. Separation on column chromatography provided compound **7** as an oil (271 mg, 70%); ^1H NMR (300 MHz, CDCl_3) δ 7.08–7.21 (5H, m), 6.78 (2H, d, $J=8.0$ Hz), 6.59 (2H, d, $J=8.0$ Hz), 4.80 (1H, d, $J=14.9$ Hz), 4.19 (1H, m), 4.10 (1H, m), 3.78 (2H, d, $J=14.9$ Hz), 3.60 (3H, s), 3.40 (1H, m), 2.39 (2H, m), 1.51–1.82 (2H, m), 0.81 (9H, s), 0.01, 0.12 (3H \times 2, s); IR (CHCl_3) 3396, 3054, 2361, 1699, 1509, 1265 cm^{-1} .

(3R,4R,5R)-3-*tert*-Butyldimethylsilyloxy-4-acetoxy-5-[2'-(*p*-methoxyphenyl)ethyl]-1-benzyl-2-pyrrolidinone (8). To a solution of **7** (156 mg, 0.34 mmol) in 3 mL of pyridine was added acetic anhydride (105 mg, 1.0 mmol), and the mixture was stirred 3 hr at room temperature. After concentration of the solution the mixture was diluted with 10 mL of EtOAc and washed with sat'd CuSO_4 solution twice and brine once, and dried over MgSO_4 . Filtration was followed by concentration and purification on silica-gel column chromatography to yield **8** (149 mg, 88%); ^1H NMR (300 MHz, CDCl_3) δ 7.13–7.29 (m, 5H), 6.88 (2H, d, $J=9.0$ Hz), 6.79 (2H, d, $J=9.0$ Hz), 5.20 (1H, m), 4.81 (1H, d, $J=13.0$ Hz), 4.40 (1H, m), 4.09 (1H, d, $J=13.0$ Hz), 3.78 (3H, s), 3.67 (1H, m), 2.41 (2H, m), 2.23 (3H, s), 1.31 (2H, m), 0.91 (9H, s), 0.10, 0.21 (3H \times 2, s); IR (CHCl_3) 2361, 1966, 1540, 1265, 896 cm^{-1} .

***N*-Benzylhomoisomycin (9).** TBAF (1 M in THF, 0.5 mL) was added to a solution of compound **8** (124 mL, 0.25 mmol) in THF. The mixture was stirred for 1 hr at room temperature, and diluted with 10 mL of EtOAc. The organic layer was washed with sat'd NH_4Cl solution twice and brine once, and dried over MgSO_4 . After concentration, the crude product was separated by silica-gel column chromatography to afford compound **9** as an oil (30 mg, 47%); $[\alpha]_{\text{D}}^{25}$ -45.4° ($c=0.35$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.12–7.29 (5H, m), 7.08 (2H, d, $J=8.6$ Hz), 6.81 (2H, d, $J=8.6$ Hz), 4.78 (1H, m), 4.20 (1H, m), 4.06 (1H, d, $J=13.1$ Hz), 3.78 (3H, s), 3.16 (1H, d, $J=13.1$ Hz), 3.22 (1H, m), 2.57 (1H, m), 2.36 (2H, m), 2.08 (3H, s), 2.01 (1H, m), 1.80 (2H, m); IR (CHCl_3) 3430, 3054, 2361, 1699, 1540, 1265 cm^{-1} ; MS (FAB, glycerol) 370 (M^+).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[3'-(*p*-methoxyphenyl)propargyl]-1-benzyl-2-pyrrolidinone (10a). A mixture of compound **3** (1.50 g, 3.18 mmol) and 4-iodoanisole (0.82 g, 3.50 mmol) in 7 mL of DMF containing CuI (30 mg, 0.016 mmol) PPh_3 (83 mg, 0.32 mmol), and K_2CO_3 (0.66 g, 4.77 mmol) was heated at 100–120 $^\circ\text{C}$ for 16 hr. After concentration under vacuum, the crude mixture was purified by silica-gel column chromatography to provide compound **10a** as an oil (1.40 g, 76%); ^1H NMR (300 MHz, CDCl_3) δ 7.09–7.30 (7H, m), 6.61 (2H, d, $J=8.9$ Hz), 4.89 (1H,

d, $J=15.0$ Hz), 4.52 (1H, d, $J=4.9$ Hz), 4.17 (1H, d, $J=15.0$ Hz), 4.06 (1H, dd, $J=7.2, 7.2$ Hz), 3.39 (1H, m), 2.39-2.60 (2H, m), 0.78 (9H, s), 0.08, 0.00, 0.01, 0.02 (3H x 4, s); IR (CHCl₃) 2930, 1712, 1606, 1509, 1250 cm⁻¹; MS (FAB, glycerol) 637 (M⁺).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[3'-(*m*-methoxyphenyl)propargyl]-1-benzyl-2-pyrrolidinone (10b), (66%): ¹H NMR (300 MHz, CDCl₃) δ 6.65-7.28 (9H, m), 4.91 (1H, d, $J=15.0$ Hz), 4.47 (1H, d, $J=4.9$ Hz), 4.18 (1H, d, $J=15.0$ Hz), 4.05 (1H, dd, $J=7.2, 7.2$ Hz), 3.77 (3H, s), 3.38 (3H, s), 3.02 (1H, m), 2.39-2.61 (2H, m), 0.78 (18H, s), 0.08, 0.00, 0.01, 0.02 (3H x 4, s).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[3'-(*o*-methoxyphenyl)propargyl]-1-benzyl-2-pyrrolidinone (10c), (70%): ¹H NMR (300 MHz, CDCl₃) δ 6.34-7.29 (9H, m), 5.11 (2H, d, $J=8.9$ Hz), 4.58 (1H, d, $J=15.0$ Hz), 4.39 (1H, d, $J=4.9$ Hz), 4.21 (1H, d, $J=15.0$ Hz), 4.01 (1H, dd, $J=7.2, 7.2$ Hz), 3.79 (3H, s), 3.58 (1H, m), 2.61-2.79 (2H, m), 0.78 (18H, s), 0.08, 0.00, 0.01, 0.02 (3H x 4, s).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[3'-(*m*-carbomethoxy-*p*-methoxyphenyl)propargyl]-1-benzyl-2-pyrrolidinone (10d), (70%): ¹H NMR (300 MHz, CDCl₃) δ 7.70 (1H, d, $J=2.1$ Hz), 7.29 (1H, d, $J=8.6$ Hz), 7.09-7.21 (5H, m), 6.76 (1H, d, $J=8.7$ Hz), 5.01 (1H, d, $J=15.0$ Hz), 4.54 (1H, d, $J=4.9$ Hz), 4.23 (1H, d, $J=15.0$ Hz), 4.12 (1H, dd, $J=7.2, 7.2$ Hz), 3.78 (3H, s), 3.65 (1H, m), δ 2.39-2.60 (2H, m), 0.78 (18H, s), 0.08, 0.00, 0.01, 0.02 (3H x 4, s).

(3R,4R,5R)-3,4-[Bis(*tert*-butyldimethylsilyloxy)-5-[3'-(*p*-methoxyphenyl)propyl]-1-benzyl-2-pyrrolidinone (11). Compound **10** (1.30 g, 2.25 mmol) was dissolved in MeOH, and 20 mg of palladium on charcoal (5%) was added to the solution. The mixture was stirred at room temperature overnight under atmospheric hydrogen pressure using balloon. After filtration and concentration, the crude product was separated on silica-gel column chromatography to yield compound **11** as an oil (820 mg, 63%): ¹H NMR (300 MHz, CDCl₃) δ 7.01-7.27 (5H, m), 6.77 (2H, d, $J=8.9$ Hz), 6.61 (2H, d, $J=8.9$ Hz), 4.78 (1H, d, $J=15$ Hz), 4.10 (1H, d, $J=6.2$ Hz), 3.87 (1H, t, $J=6.7$ Hz), 3.79 (1H, d, $J=15$ Hz), 3.65 (3H, s), 2.20-2.51 (2H, m), 1.20-1.51 (4H, m), 0.73, 0.79 (9H x 2, s), -0.20, -0.11, 0.29, 0.11 (3H x 4, s); IR (CHCl₃) 1710, 1612, 1464, 1249 cm⁻¹.

(3R,4R,5R)-3,4-Dihydroxy-5-[3'-(*p*-methoxyphenyl)propyl]-1-benzyl-2-pyrrolidinone (12). To a solution of **11** (720 mg, 1.20 mmol) in 5 ml THF was added TBAF (1 M in THF, 3 mL), and the mixture was stirred for 3 hr at room temperature and quenched by addition of water. Dilution of the mixture with 20 mL of EtOAc was followed by washing with sat'd NH₄Cl solution twice and brine once. After drying over MgSO₄ filtration, and concentration, the crude product was purified by silica-gel to afford **12** as an oil (350 mg, 82%): ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.25 (5H, m), 7.00 (2H, d, $J=8.9$ Hz), 6.79 (2H, d, $J=8.9$ Hz), 4.89 (2H, d, $J=15.1$ Hz), 4.47 (1H, m), 4.28 (1H, m), 4.00 (1H, d, $J=15.1$ Hz), 3.79 (3H, s), 3.46 (1H, m), 2.51 (2H, m), 1.79-2.00 (2H, m); IR (CHCl₃) 3396, 3054, 1734, 1652, 1558, 1456 cm⁻¹; MS (FAB, glycerol) 342 (M⁺).

(3R,4R,5R)-3-*tert*-Butyldimethylsilyloxy-4-hydroxy-5-[3'-(*p*-methoxyphenyl)propyl]-1-benzyl-2-pyrrolidinone

(13). Compound **12** (100 mg, 0.28 mmol) was dissolved in CH₂Cl₂, and TBSCl (42 mg, 0.28 mmol) was added to the solution. The mixture was stirred at room temperature overnight. After the usual work-up procedure, the crude product was separated to afford compound **13** as an oil (50 mg, 38%): ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.55 (5H, m), 6.90 (2H, d, $J=8.7$ Hz), 6.81 (2H, d, $J=8.9$ Hz), 4.92 (1H, d, $J=15.1$ Hz), 4.30 (1H, d, $J=6.3$ Hz), 4.11 (1H, t), 3.81 (1H, d, $J=6.3$ Hz), 3.71 (3H, s), 3.38-3.53 (1H, m), 2.41-2.50 (2H, m), 1.48-1.59 (4H, m), 0.90 (9H, s), -0.11, 0.13, 0.31 (3H x 3, s); IR (CHCl₃) 3435, 2930, 1753 cm⁻¹.

(3R,4R,5R)-3-*tert*-Butyldimethylsilyloxy-4-acetoxy-5-[3'-(*p*-methoxyphenyl)propyl]-1-benzyl-2-pyrrolidinone (14). The same procedure as that of **7** was applied to the compound **13** (86 mg, 0.18 mmol). Compound **14** was obtained as an oil (74 mg, 78%): ¹H NMR (300 MHz, CDCl₃) δ 6.90-7.21 (5H, m), 6.84 (2H, d, $J=8.5$ Hz), 6.61 (2H, d, $J=8.5$ Hz), 4.90 (1H, dd, $J=6.1, 6.4$ Hz), 4.81 (1H, d, $J=15.0$ Hz), 4.09 (1H, t, $J=6.1$ Hz), 3.79 (1H, d, $J=15.0$ Hz), 3.71 (3H, s), 3.60 (1H, m), 2.21 (2H, m), 1.80 (3H, s), 1.21-1.44 (4H, m), 0.71 (9H, s), -0.11, 0.12 (3H x 2, s); IR (CHCl₃) 2931, 1713, 1511, 1244 cm⁻¹.

(3R,4R,5R)-1-Benzyl-2-[3'-(*p*-methoxyphenyl)propyl]-3-acetoxy-4-hydroxypyrrolidine (15). The same procedure as that of **8** was applied to the compound **14**. Compound **15** (7 mg, 28% in two step) was obtained as an oil: ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.42 (5H, m), 7.12 (2H, d, $J=8.5$ Hz), 6.8 (2H, d, $J=8.5$ Hz), 4.80 (1H, dd, $J=6.3, 2.2$ Hz), 4.11 (1H, t, $J=6.3$ Hz), 3.95 (1H, d, $J=13.1$ Hz), 3.80 (3H, s), 3.21 (1H, d, $J=13.1$ Hz), 3.15 (1H, d, $J=8.9$ Hz), 2.80 (1H, bs), 2.60-2.70 (2H, m), 2.51 (1H, t, $J=5.1$ Hz), 2.12 (1H, t, $J=7.1$ Hz), 2.01 (3H, s), 1.60-1.80 (4H, m); IR (CHCl₃) 3516, 2922, 1735, 1360, 1045 cm⁻¹.

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