DIOLMYCINS, NEW ANTICOCCIDIAL AGENTS PRODUCED BY *Streptomyces* sp.

II. STRUCTURE ELUCIDATION OF DIOLMYCINS A1, A2, B1 AND B2, AND SYNTHESIS OF DIOLMYCIN A1

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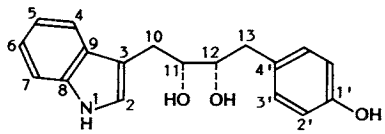
The structures of diolmycins A1, A2, B1 and B2, novel anticoccidial agents, were determined by spectroscopic analyses. Diolmycins A1 and A2 are stereoisomers with the structure of 1-(3-indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol. From the chemical synthesis of the *erythro*-isomer, the relative configurations of diolmycins A1 and A2 were determined to be the *erythro*- and *threo*-isomers, respectively. The stereoisomers, diolmycins B1 and B2, were also deduced to be *erythro*- and *threo*-1,4-di-(*p*-hydroxyphenyl)-2,3-butanediol, respectively.

In the course of our screening for anticoccidial agents, diolmycins A1, A2, B1 and B2 (Fig. 1) were isolated from the fermentation broth of *Streptomyces* sp. WK-2955. Taxonomy of the producing strain, fermentation, isolation and physico-chemical and biological characteristics of the diolmycins were reported in the preceding paper[1]. In this report, the structure elucidation of diolmycins A1, A2, B1 and B2, and the chemical synthesis of diolmycin A1 are described.

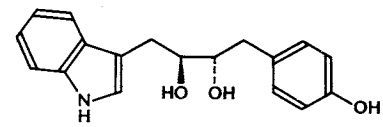
Structure Elucidation of Diolmycins A1 and A2

The molecular formula of diolmycin A1 (**1**) was determined to be $C_{18}H_{19}NO_3$ (*m/z* found 297.1363, calcd 297.1364) by HREI-MS analysis. The ^1H NMR spectrum of **1** showed 15 proton signals in CD_3OD (Table 1) and 19 proton signals in DMSO-d_6, suggesting the presence of four exchangeable protons. The ^{13}C NMR spectrum showed 16 carbon signals (Table 1), but revealed the presence of 18 carbons from the peak intensity (each of δ 131.8 and 116.3 ppm signals seemed to contain two carbons). The DEPT

Fig. 1. Structures of diolmycins A1 (**1**), A2 (**2**), B1 (**3**) and B2 (**4**).



Diolmycin A1 (**1**)



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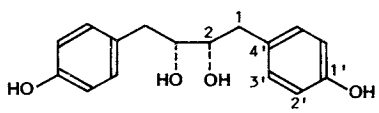
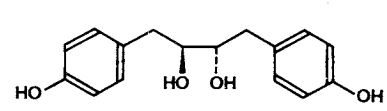


Diolmycin B1 (**3**)



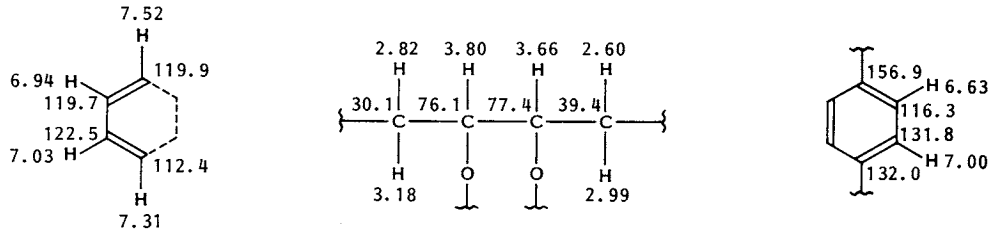
Diolmycin B2 (**4**)

Table 1. ^{1}H and ^{13}C NMR chemical shifts of diolmycins A1 (**1**) and A2 (**2**).

Carbon No.	1			2	
	^{13}C[a]	^{1}H[a]	^{1}H[b]	^{13}C[a]	^{1}H[a]
1-NH			10.73 (1H, s)		
C-2	124.5	7.09 (1H, s)	7.12 (1H, s)	124.4	7.07 (1H, s)
C-3	113.2			113.1	
C-4	119.9	7.56 (1H, d, J=8.0 Hz)	7.52 (1H, d, J=7.8 Hz)	119.8	7.46 (1H, d, J=7.9 Hz)
C-5	119.7	6.97 (1H, dd, J=8.0, 7.8 Hz)	6.94 (1H, dd, J=7.8, 7.0 Hz)	119.8	6.94 (1H, dd, J=8.0, 7.9 Hz)
C-6	122.5	7.07 (1H, dd, J=8.0, 7.8 Hz)	7.03 (1H, dd, J=7.9, 7.0 Hz)	122.4	7.02 (1H, dd, J=8.0, 8.0 Hz)
C-7	112.4	7.31 (1H, d, J=8.0 Hz)	7.31 (1H, d, J=7.9 Hz)	112.4	7.30 (1H, d, J=8.0 Hz)
C-8	138.4			138.4	
C-9	129.5			129.3	
C-10	30.1	2.82 (1H, dd, J=14.9, 9.0 Hz), 3.18 (1H, dd, J=14.9, 4.0 Hz)	2.45 (1H, dd, J=14.3, 9.0 Hz), 3.03 (1H, dd, J=14.3, 3.8 Hz)	30.9	2.89 (1H, dd, J=14.3, 7.6 Hz), 3.05 (1H, dd, J=14.3, 6.7 Hz)
C-11	76.1	3.80 (1H, ddd, J=9.0, 5.4, 4.0 Hz)	3.56 (1H, m)	74.3	3.79 (1H, ddd, J=7.6, 6.7, 2.2 Hz)
C-11-OH			4.55 (2H, s)		
C-12-OH					
C-12	77.4	3.66 (1H, ddd, J=9.1, 5.4, 3.9 Hz)	3.42 (1H, m)	75.7	3.66 (1H, ddd, J=8.0, 6.0, 2.2 Hz)
C-13	39.4	2.60 (1H, dd, J=14.0, 9.1 Hz), 2.99 (1H, dd, J=14.0, 3.9 Hz)	2.65 (1H, dd, J=14.0, 8.0 Hz), 2.85 (1H, dd, J=14.0, 3.9 Hz)	40.4	2.69 (1H, dd, J=13.4, 8.0 Hz), 2.79 (1H, dd, J=13.4, 6.0 Hz)
C-1′	156.9			156.9	
C-1′-OH			9.07 (1H, s)		
C-2′	116.3	6.69 (2H, d, J=8.0 Hz)	6.63 (2H, d, J=8.2 Hz)	116.3	6.64 (2H, d, J=8.7 Hz)
C-3′	131.8	7.07 (2H, d, J=8.0 Hz)	7.00 (2H, d, J=8.2 Hz)	131.6	6.98 (2H, d, J=8.7 Hz)
C-4′	132.0			131.6	

[a] Measured in CD_3OD.
[b] Measured in DMSO-d_6.

Fig. 2. Partial structures I, II and III for diolmycin A1.



I II III

Fig. 3. ^{13}C-^{1}H long range COSY of diolmycin A1.

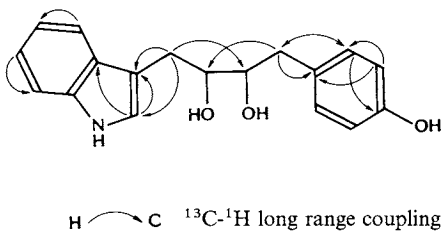
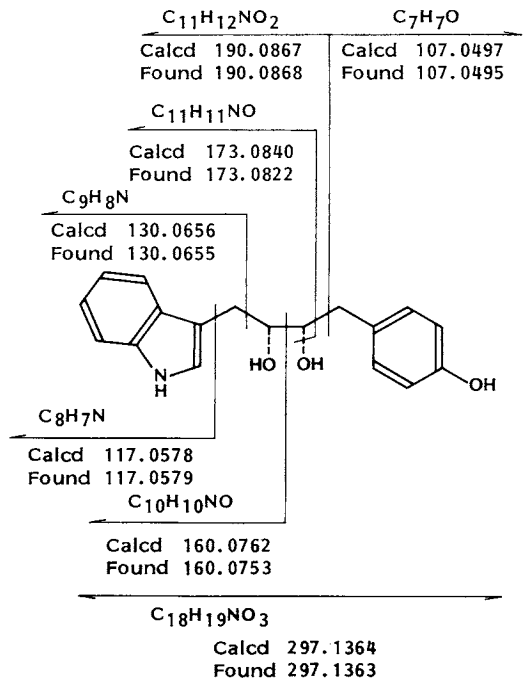


Fig. 4. HREI-MS analysis of diolmycin A1.



spectrum indicated the presence of two $-CH_2-$, two $-O-CH-$, nine $-CH=$ and five quaternary carbons. The connection of protons and carbons was confirmed by the ^{13}C-^{1}H COSY spectrum as shown in Table 1. Analysis of the ^{1}H-^{1}H COSY spectrum revealed the three partial structures I, II and III (Fig. 2). The fragment ion peak at *m/z* 130 in the EI-MS and UV spectra suggested the presence of an indole moiety in **1**. The chemical shifts of ^{1}H and ^{13}C NMR of the partial structure I were consistent with those of a 3-substituted indole[2]. The chemical shifts of the partial structure III indicated the presence of a *p*-phenol moiety. ^{13}C-^{1}H long range couplings of ^{2}J and ^{3}J observed in the ^{13}C-^{1}H long range COSY spectrum are shown in Fig. 3. This structure was also explainable by the fragment ion peak analysis of HREI-MS (Fig. 4). Consequently, the structure of **1** was determined to be 1-(3-indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol (Fig. 1).

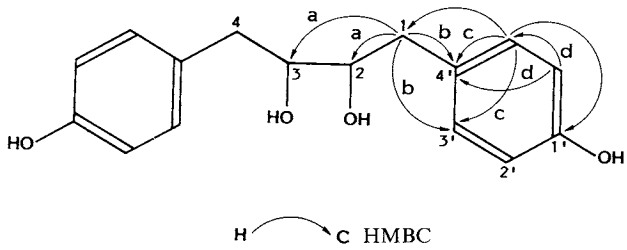
The same molecular formula $C_{18}H_{19}NO_3$ as that of **1** was determined for diolmycin A2 (**2**) (*m/z* found 297.1361) by HREI-MS analysis. Various spectral data (EI-MS, various NMR measurements and UV) of **2** were very similar to those of **1** (Table 1). The resulting plane structure of **2** was the same as **1**, suggesting that diolmycins A1 and A2 are stereoisomers. In fact, the ^{1}H coupling constants corresponding to the two chiral carbons (C-11 and C-12) were different between **1** and **2** (Table 1). The respective coupling constants between the vicinal 11-H and 12-H protons of **1** and **2** were 5.4 and 2.2 Hz, suggesting that the respective diols have *erythro*- and *threo*-configurations[3~5]. The stereochemistry of **1** was confirmed by the total synthesis of **1** as described below.

Table 2. ^{1}H and ^{13}C NMR chemical shifts of diolmycins B1 (**3**) and B2 (**4**).

Carbon No.	**3**		**4**	
	^{13}C	^{1}H	^{13}C	^{1}H
C-1, 4	39.6	2.55 (2H, dd, J=14.0, 8.5 Hz), 2.93 (2H, dd, J=14.0, 3.8 Hz)	40.3	2.66 (2H, dd, J=13.2, 7.3 Hz), 2.77 (2H, dd, J=13.2, 5.6 Hz)
C-2, 3	77.3	3.58 (2H, ddd, J=8.5, 5.2, 3.8 Hz)	75.5	3.56 (2H, ddd, J=7.3, 5.6, 2.5 Hz)
C-1′	156.9		156.9	
C-2′	116.3	6.69 (4H, d, J=8.5 Hz)	116.3	6.663 (4H, d, J=8.5 Hz)
C-3′	131.8	7.05 (4H, d, J=8.5 Hz)	131.6	6.959 (4H, d, J=8.5 Hz)
C-4′	131.8		131.6	

Measured in CD_3OD.

Fig. 5. HMBC analysis of diolmycin B1.



a) Since C-2 and C-3 have the same chemical shifts of ^{13}C NMR, either or both ^{13}C-^{1}H long range couplings are available. b, c, d) Since C-3′ and C-4′ have the same chemical shifts of ^{13}C NMR, either or both ^{13}C-^{1}H long range couplings are available.

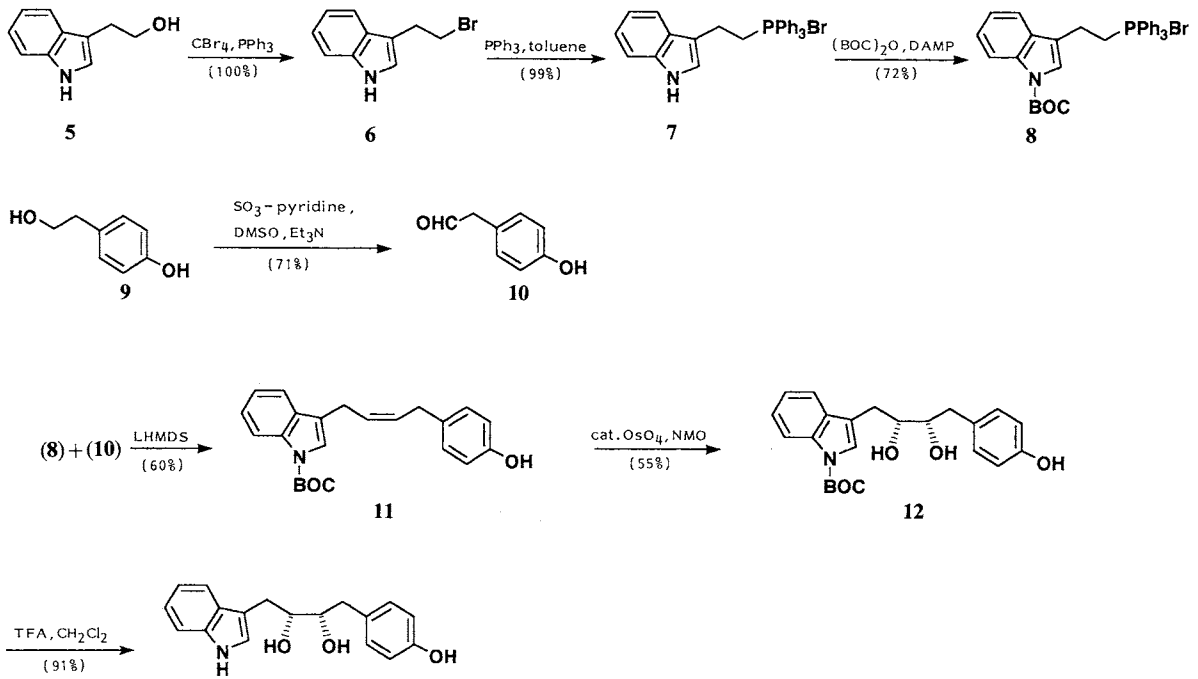
Structure Elucidation of Diolmycins B1 and B2

The molecular formulas of diolmycins B1 (**3**) and B2 (**4**) were determined to be $C_{16}H_{18}O_4$ (*m/z* found **3**; 274.1207, **4**; 274.1187, calcd 274.1204) by HREI-MS analysis. The UV spectra of **3** and **4** had the same maxima at 223, 277 and 285 nm[1]. The ^{1}H and ^{13}C NMR spectra of **3** and **4** (Table 2) showed 7 proton signals and 6 carbon signals, but revealed the presence of 8 carbons from the peak intensity. Taking the molecular formulas into consideration, it was expected that they possess symmetrical structures. ^{13}C-^{1}H long range couplings of ^{2}J and ^{3}J observed in the HMBC spectrum of **3** are shown in Fig. 5. Furthermore, in comparison with various NMR data of **1** and **2**, the structures of **3** and **4** were determined to be 1,4-di-(1-hydroxyphenyl)-2,3-dihydroxybutane (Fig. 1). The relative configurations of **3** and **4** were also deduced to be *erythro* and *threo* from the coupling constants between their vicinal *O*-methine protons (**3**, 5.2 Hz; **4**, 2.5 Hz).

Synthesis of Diolmycin A1

The deduced relative structure of **1** was confirmed by synthesis. The synthesis of **1** was accomplished *via* stereoselective Wittig reaction with 3-(1-*tert*-butoxycarbonylindole)ethyltriphenyl phosphonium bromide (**8**) and *p*-hydroxyphenylacetaldehyde (**10**) followed by osmium tetroxide oxidation as outlined in Scheme 1. Indoleethanol (**5**) was treated with carbon tetrabromide and triphenylphosphine to obtain the bromide (**6**) quantitatively. Compound **6** was refluxed with triphenylphosphine in toluene to obtain the phosphonium salt (**7**) quantitatively. Compound **7** was protected with *tert*-butoxycarbonyl (BOC) to prevent the oxidation

Scheme 1. Chemical syntheses of *dl*-diolmycin A1.



PPh_3: triphenylphosphine, BOC: *tert*-butoxycarbonyl, DAMP: 4-dimethylaminopyridine, LHMDS: lithium *bis*(trimethylsilyl)amide, NMO: 4-methylmorpholine *N*-oxide, TFA: trifluoroacetic acid.

of indole in treatment of BOC anhydride and 4-dimethylaminopyridine (DMAP) in acetonitrile[6] in moderate yield. *p*-Hydroxyphenylacetaldehyde (**10**) was prepared by oxidation of *p*-hydroxylphenylethanol (**9**) by treatment with SO_3-pyridine complex in DMSO in 71%. The Wittig reaction was carried out between 3-(1-*tert*-butoxycarbonylindole)ethyltriphenylphosphonium bromide (**8**) and *p*-hydroxyphenylacetaldehyde (**10**). For the formation of the unstable yilid, **8** was added to 1.5 equivalents of lithium *bis* (trimethylsilyl)amide (LHMDS) at 0°C for 30 minutes. The resulting yilid quenched by **10** at 0°C gave the (*Z*)-olefin (**11**) predominantly[7] in moderate yield. Coupling constants between olefinic protons of the olefin (**11**) were 10.7 Hz by decoupling. The resulting (*Z*)-olefin (**11**) was oxidized by catalytic osmium tetroxide and 4-methylmorpholine *N*-oxide (NMO) in dioxane[8] to yield the *erythro*-diol (**12**) in 55%. Finally, the *tert*-butoxycarboxyl protecting group of the indole was removed by treatment with trifluoroacetic acid (TFA) in dichloromethane[9] to obtain *dl*-diolmycin A1 (**13**) in high yield. Synthetic *dl*-diolmycin A1 was identical in ^{1}H NMR, IR, and MS with natural diolmycin A1 (**1**).

The first total synthesis of *dl*-diolmycin A1 has been achieved and confirmed the deduced structure including the relative stereochemistry. The asymmetric synthesis of (−)-diolmycin A1 will be reported to determine the absolute stereochemistry of diolmycin A1.

Experimental

NMR spectra were measured on a JEOL EX-270 or a Varian XL-400 spectrometer in $CDCl_3$ or CD_3OD. Chemical shifts are shown with reference to CD_3OD as 49.8 ppm and 3.3 ppm or to DMSO-d_6 as 39.5 ppm and 2.5 ppm. IR spectra were measured on a JASCO A-102 spectrometer. Column chromatography was performed on silica gel 60 (Merck 230~400 mesh). Preparative TLC was performed on silica gel (Merck 60 PF 254) of 0.5 mm thickness. Mass spectra were obtained on a JEOL D-100 and a DX-300 spectrometer at 20 eV.

Chemical Synthesis

3-Indoleethyl Bromide (6)

To a solution of 3-indoleethanol (**5**) (3.20 g, 19.9 mmol) in dry THF (40 ml), carbon tetrabromide (7.96 g, 23.82 mmol) and triphenylphosphine (6.30 g, 23.82 mmol) was added and the reaction mixture was stirred at room temperature under argon for 15 minutes. The solvent was evaporated at 20°C and the resulting residue was purified by flash chromatography (*n*-hexane-ethyl acetate=15:1) to obtain the 3-indoleethyl bromide (**6**) (4.43 g, 100%). EI-MS *m/z* 223 (M^+). HREI-MS calcd for $C_{10}H_{10}NBr$: 222.9997, found: 222.9998. IR ($CHCl_3$) cm^{-1} 3470 and 3000. ^{1}H NMR ($CDCl_3$) δ 3.22~3.45 (2H, m), 3.53~3.78 (2H, m), 7.05~7.71 (5H, m), 8.01 (1H, br s).

(3-Indoleethyl)triphenylphosphonium Bromide (7)

To a solution of **6** (4.43 g, 19.9 mmol) in dry toluene (40 ml), triphenylphophine (6.30 g, 23.82 mmol) was added and the reaction mixture was refluxed for 18 hours under argon. The solvent was evaporated and the resultant residue after washing with ether (200 ml) was purified by flash chromatography (ethyl acetate-methanol=2:1) to give the yellow powder of (3-indoleethyl)triphenylphosponium bromide (**7**) (9.60 g, 99%). FAB-MS *m/z* 486 (M^+). IR ($CHCl_3$) cm^{-1} 3470 and 2940. ^{1}H NMR ($CDCl_3$) δ 3.10~3.27 (2H, m), 4.10~4.22 (2H, m), 7.00~7.75 (20H, m), 8.00 (1H, br s).

3-(1-*tert*-Butoxycarbonyl)indoleethyltriphenylphosphonium Bromide (8)

To a solution of **7** (5.22 g, 10.7 mmol) in acetonitrile (40 ml), di-*tert*-butyl dicarbonate (7.05 g, 32.3 mmol) and 4-dimethylaminopyridine (1.31 g, 10.7 mmol) were added and the reaction mixture was stirred at room temperature for 5 hours under argon. The reaction mixture was concentrated (100 ml), dried over Na_2SO_4 and the solvent was evaporated. The resultant residue was purified by flash

chromatography (ethyl acetate - ethanol = 5 : 1) to obtain the orange powder of 3-(1-*tert*-butoxycarbonyl)-indoleethyltriphenylphosphonium bromide (**8**) (4.53 g, 72%). FAB-MS *m/z* 586 (M^+). IR ($CHCl_3$) cm^{-1} 2940 and 1725. ^1H NMR ($CDCl_3$) δ 1.64 (9H, s), 3.15~3.28 (2H, m), 4.10~4.25 (2H, m), 7.05~8.10 (20H, m).

p-Hydroxyphenylacetaldehyde (**10**)

To a solution of *p*-hydroxyphenyl ethanol (**9**) (4.14 g, 30 mmol) in DMSO (60 ml) and triethylamine (25.1 ml, 180 mmol), sulfur trioxide-pyridine complex (14.32 g, 90 mmol) in DMSO (60 ml) was added dropwise over 15 minutes and the reaction mixture was stirred at room temperature under argon. After 1 hour the reaction was quenched by pouring into the cold water (200 ml), the mixture was extracted with CH_2Cl_2 (200 ml × 3). The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The resultant residue was purified by flash chromatography (*n*-hexane - ethyl acetate = 5 : 1) to obtain *p*-hydroxyphenyl acetaldehyde (**10**) (2.89 g, 71%). EI-MS *m/z* 136 (M^+). HREI-MS calcd for $C_8H_8O_2$: 136.0525, found: 136.0525. IR ($CHCl_3$) cm^{-1} 3500~3100, 3000 and 1720. ^1H NMR ($CDCl_3$) δ 3.55~3.92 (2H, m), 5.30~5.62 (1H, br s), 6.63~7.50 (4H, m), 9.80 (1H, s).

(*Z*)-1-(1-*tert*-Butoxycarbonyl-3-indolyl)-4-(*p*-hydroxyphenyl)-2-butene (**11**)

To a solution of 3-(1-*tert*-butoxycarbonyl)indoleethyltriphenylphosphonium bromide (**8**) (4.13 g, 7.0 mmol) in dry THF (7 ml), 1.0 M lithium *bis*(trimethylsilyl)amide (7.7 ml, 7.7 mmol) in *n*-hexane was added dropwise over 10 minutes at 0°C under argon and the mixture was stirred at 0°C for 30 minutes. A solution of *p*-hydroxyphenylacetaldehyde (**10**) (863 mg, 6.3 mmol) in dry THF (4 ml) was added dropwise to the mixture over 10 minutes at 0°C and the reaction mixture was stirred at 0°C for 20 minutes and warmed to room temperature for 20 minutes. The reaction mixture was quenched with a saturated NH_4Cl solution (30 ml) and extracted with ethyl acetate (30 ml × 3). The ethyl acetate extract was dried over Na_2SO_4, filtered and evaporated. The resultant residue was purified by flash chromatography (*n*-hexane - ethyl acetate = 10 : 1) to obtain a yellow oil of (*Z*)-1-(1-*tert*-butoxycarbonyl-3-indolyl)-4-(*p*-hydroxyphenyl)-2-butene (**11**), (1.38 g, 60%). EI-MS *m/z* 363 (M^+) HREI-MS calcd for $C_{23}H_{25}NO_3$: 363.1834, found: 363.1836, IR ($CHCl_3$) cm^{-1} 3350~3100, 3000~2900 and 1725. ^1H NMR ($CDCl_3$) δ 1.66 (9H, s), 3.48 (2H, d, J = 6 Hz), 3.54 (2H, d, J = 6 Hz), 5.20 (1H, br s), 5.68~5.82 (2H, m), coupling constants between olefinic protons were 10.7 Hz by decoupling, 6.85 (2H, d, J = 9 Hz), 7.09 (2H, d, J = 9 Hz), 7.10~7.55 (4H, m), 8.00~8.22 (1H, m).

erythro-1-(1-*tert*-Butoxycarbonyl-3-indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol (**12**)

A mixture of **11** (360 mg, 0.99 mmol), 4-methylmorpholine *N*-oxide (422 mg, 3.57 mmol) and 0.05 M osmium tetroxide solution in *tert*-BuOH (596 μl, 0.30 mmol) in THF - H_2O (10 : 1) was stirred at room temperature in the dark for 3 hours. After addition of solid Na_2SO_3 (50 mg), the mixture was diluted with CH_2Cl_2 (40 ml), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The oily residue was purified by flash chromatography (*n*-hexane - ethyl acetate = 5 : 1) to obtain *erythro*-1-(1-*tert*-butoxycarboxyl-3-indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol (**12**) (236 mg, 60%). EI-MS *m/z* 397 (M^+), HREI-MS calcd for $C_{23}H_{27}NO_5$: 397.1888, found 397.1855, IR ($CHCl_3$) cm^{-1} 3550~3100, 3000~2850 and 1720. ^1H NMR ($CDCl_3$) δ 1.68 (9H, s), 2.30 (3H, br s), 2.65~3.10 (4H, m), 3.88 (2H, m), 6.70 (2H, d, J = 8.3 Hz), 7.05 (2H, d, J = 8.3 Hz), 7.10~7.60 (4H, m), 8.00~8.22 (1H, m).

erythro-1-(3-Indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol (**13**)

To a solution of **12** (17 mg, 0.043 mmol) in CH_2Cl_2 (1.0 ml) at 0°C under argon, trifluoroacetic acid (0.5 ml) was added dropwise and the mixture was stirred at 0°C for 1.3 hours. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4, filtered and evaporated. The resultant residue was purified by preparative TLC ($CHCl_3$ - methanol = 5 : 1) to obtain *erythro*-1-(3-indolyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol (**13**) (11.5 mg, 91%). EI-MS *m/z* 297 (M^+), HREI-MS calcd for $C_{18}H_{19}NO_3$: 297.1364, found: 297.1364, IR ($CHCl_3$) cm^{-1} 3500~3100 and 3000~2850, ^1H NMR (CD_3OD) δ 2.60 (1H, dd, J = 14.0, 9.1 Hz), 2.82 (1H, dd, J = 14.9, 9.0 Hz), 2.99 (1H, dd, J = 14.0, 3.9 Hz), 3.18 (1H, dd, J = 14.9, 4.0 Hz), 3.66 (1H, ddd, J = 9.1, 5.4, 3.9 Hz), 3.80 (1H, ddd, J = 9.0, 5.4, 4.0 Hz), 6.69 (2H, d, J = 8.0 Hz), 6.97~7.09 (5H, m), 7.31 (1H, d,

J=8.0 Hz), 7.56 (1H, d, J=8.0 Hz).

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