Selective Deoxygenation and *O*-Methylation of Benanomicin A: Synthesis of 9-Deoxy-, 9-*O*-Methyl- and 14-*O*-Methylbenanomicin A

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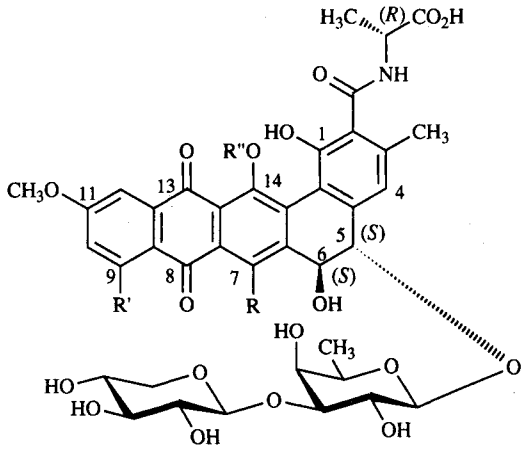
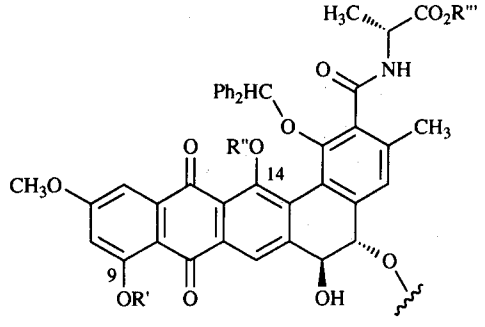
The selective modifications of phenolic hydroxy groups in the chromophore of benanomicin A are described. Hydride reduction of 9-*O*-tosylate with sodium borohydride/nickel chloride led to 9-deoxybenanomicin A. Methylation of 1-*O*-diphenylmethylbenanomicin A diphenylmethyl ester with sodium hydride/iodomethane gave 9-*O*-methyl derivative and with HÜNIG's base/diazotrimethylsilylmethane afforded the 14-*O*-methyl derivative. These compounds showed the diminished activity against fungi.

A potent antifungal antibiotic, benanomicin A (**1**), was isolated from the culture broth of *Actinomadura spadix* MH193-16F4[1,2] and the absolute structure was elucidated by various NMR and degradation experiments[3]. Under experiments for the structure-activity relationships of **1**, we reported the chemical replacement of the D-alanine moiety in **1** by a variety of amino acids through desalaninebenanomicin A[4]. 7-Hydroxybenanomicin A (**2**) was produced by a mutant strain of *A. spadix* MH193-16F4 No. M20-1[5]. Although the absolute configuration of **2** was the same as that of **1**, the antifungal activity of **2** was completely absent. This was attributed to the conformational difference of the aglycon, *i. e.* the molecular helicity of dihydrobenzo[*a*]naphthacenequinone, between **1** and **2**. In the ^{1}H NMR spectra, $J_{5,6}$ of **1** was 10.2 Hz and that of **2** was 3.0 Hz. Furthermore, the CD spectrum of **2** showed an opposite Cotton effect curve to that of **1**[5].



	R	R'	R"
Benanomicin A (**1**)	H	OH	H
7-Hydroxybenanomicin A (**2**)	OH	OH	H
9-Deoxybenanomicin A (**3**)	H	H	H
9-*O*-Methylbenanomicin A (**4**)	H	OCH_3	H
14-*O*-Methylbenanomicin A (**5**)	H	OH	CH_3



	R'	R"	R"'
6	H	H	$CHPh_2$
7	Ts	H	$CHPh_2$
8	CH_3	H	$CHPh_2$
9	CH_3	H	H
10	H	CH_3	$CHPh_2$

These interesting results prompted us to modify the hydroxy groups on the chromophore of **1**. We describe here the synthesis of 9-deoxy-, 9-*O*-methyl- and 14-*O*-methylbenanomicin A from **1**. It was felt worthwhile to modify one of the three phenolic hydroxyl groups selectively in the complex aglycon of **1** to elucidate the structure-activity relationships.

9-Deoxybenanomicin A (3)

Many methods for the mild and general deoxygenation of phenolic hydroxy groups have been described[6,7]. We accomplished the selective deoxygenation of the hydroxy group at the C-9 position in the highly functionalized benanomicin chromophore through the sodium hydride/nickel chloride reduction of its sulfonate by the method of WANG[8].

Treatment of **1** with diazodiphenylmethane in a mixture of *N*,*N*-dimethylformamide (DMF) and methanol at 40°C gave 1-*O*-diphenylmethylbenanomicin A diphenylmethyl ester (**6**) in 34% yield along with benanomicin A diphenylmethyl ester. The position of the diphenylmethyl ether moiety in **6** has been confirmed by the NMR spectra. The ^{1}H NMR spectrum of **6** clearly showed two hydrogen-bonded phenolic proton signals (9- and 14-OHs) at δ 12.90 and 13.21 because the interaction between 1-OH and 14-OH disappeared. Tosylation of **6** with *p*-toluenesulfonyl chloride and potassium carbonate in dry acetone gave a chromatographically pure mono-tosylate (**7**) in 50% yield. In the ^{1}H NMR spectrum of **7** the methyl protons of the tosyl group resonated at δ 2.20 and a resonance due to a phenolic OH at the 9-position disappeared. Hydride replacement of the aryl tosylate of **7** by sodium borohydride and nickel chloride[8] in a mixture of methanol and chloroform at -78°C to room temperature followed by hydrolysis of benzhydryl ester gave 9-deoxybenanomicin A (**3**). During the hydride reduction of **7**, part of the tosyl group was simply cleaved to afford starting **6** and the 1-*O*-diphenylmethyl group was completely removed. In the ^{1}H NMR spectrum of **3**, the new aromatic proton signal, 9-H, appeared at δ 8.19 as a doublet ($J_{9,10}$= 8.6 Hz) and the 10-H signal at 7.48 changed to a double doublet ($J_{9,10}$=8.6 and $J_{10,12}$=2.6 Hz). The doublets due to 5- and 6-H (δ 4.51 and 4.59 respectively) with J=10.2 Hz indicated that **3** has the same helical pitch as **1**. The ^{13}C NMR spectrum of **3** showed that C-9 (resonating at δ 129.5) is attached to a proton (by DEPT) and C-8 (δ 180.1), one of the quinone carbons, was shifted upfield compared with **1**.

9-*O*-Methyl- and 14-*O*-Methylbenanomicin A (4 and 5)

Compound **6** was treated with sodium hydride and iodomethane in DMF to afford a 9-*O*-methyl-bis(diphenylmethyl) derivative (**8**) selectively. During the methylation the product could not be detected on TLC, because the Rf value of the product was almost the same as that of **6**. After hydrolysis of the diphenylmethyl ester of the mixture with alkali, 9-*O*-methyl-1-*O*-diphenylmethyl ether (**9**) was obtained by chromatographic separation on silica-gel in 38% yield in two steps. Hydrogenolysis of **9** with 10% Pd on carbon in ethanol gave 9-*O*-methylbenanomicin A (**4**). An additional methoxy group was shown by ^{1}H and ^{13}C NMR spectroscopy of **4**. In addition, the carbon signal due to the 9-position (at δ 162.5) shifted upfield and the C-8 signal (δ 178.4), one of the quinone carbons, also shifted upfield compared with those of **1**. An HMBC experiment clearly confirmed the structure of **4**.

Meanwhile, **6** was reacted with HÜNIG's base and diazo(trimethylsilyl)methane in a mixture of methanol and acetonitrile to give a 14-*O*-methyl-bis(diphenylmethyl) derivative (**10**) in 87% yield. Successive removal of benzhydryl groups of **10** with alkali and H_2/Pd-black afforded **5**. In the ^{1}H NMR spectrum of **5**, a new methoxy group resonance was observed at δ 3.68 and protons of the 5- and 6-positions resonated at δ 4.58 and 4.62 with J=10 Hz. The ^{13}C NMR spectrum of **5** indicated that the quinone carbon at the 13-position (δ 180.1) has hydrogen-bonding no longer.

Antifungal Activity of 3, 4 and 5

The minimum inhibitory concentrations of **3** and **1** against fungi are shown in the Table. Deoxygenation at the 9-position of **1** produced a sharp fall in activities. *O*-Methylbenanomicin A (**4** and **5**) showed no activity against *Candida albicans* by the disk assay on agar plate

Table 1. Antifungal activity of 9-deoxybenanomicin A (**3**) and benanomicin A (**1**).

Microorganism	MIC (μg/ml)	
	3	**1**
Candida albicans 3147	100	6.25
C. tropicalis F-1	100	6.25
C. pseudotropicalis F-2	12.5	3.13
Saccharomyces cerevisiae F-7	12.5	3.13
Cryptococcus neoformans F-10	50	1.56
Aspergillus niger F-16	>100	12.5

at the concentration of 1000 μg/ml.

It has been reported that the antifungal activity of benanomicin A and analogs is due to the recognition of mannan on the fungal cell surface in the presence of calcium ion[5,9~11]. In the binding assay of the compounds synthesized here to *Saccharomyces cerevisiae*, **3** and **4** showed weak binding-activities, 63% and 15% of that of **1** respectively, and **5** did not bind to the test organism under the test conditions.

Thus, the presence of phenolic hydroxy groups, 9- and 14-OH, of **1** is essential for the exertion of potent activity against fungi.

Experimental

General

Mass spectra (FAB-MS) were measured in a Jeol JMX-SX102 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in a Jeol JNM-GX400 or JNM-LA400 spectrometer in DMSO-d_6 at 50°C.

1-*O*-Diphenylmethylbenanomicin A Diphenylmethyl Ester (**6**)

To a solution of **1** (2.0 g) in DMF (30 ml) and MeOH (30 ml) was added a solution of diazodiphenylmethane (1.6 g) in hexane. The resulting solution was stirred at 40°C overnight and concentrated to remove MeOH and hexane. The residual solution was poured into water (300 ml). The resulting precipitates were filtered. The solid was triturated with EtOAc (100 ml × 3) and filtered. The combined solution was concentrated and purified by a silica-gel column chromatography ($CHCl_3$/MeOH 4:1) to give **6** (943 mg). FAB-MS (negative) *m/z* 1158 ($[M-H]^-$). ^{1}H NMR δ 1.21 (3H, d, J=7.5 Hz, 6″-H), 1.25 (3H, d, J=6.0 Hz, 3′-H), 2.25 (3H, s, 16-H), 3.04~3.17 (3H, 2‴-H, 3‴-H and 5‴-Ha), 3.30 (1H, m, 4‴-H), 3.50~3.63 (3H, 3″-H, 4″-H and 5″-H), 3.70 (1H, dd, J=11.3 and 6.0 Hz, 5‴-Hb), 3.90 (1H, dd, J=11.1 and 2.5 Hz, 2″-H), 3.96 (3H, s, 11-OCH_3), 4.28 (1H, d, J=10.6 Hz, 5-H), 4.38 (1H, br q, J=7.5 Hz, 2′-H), 4.40 (1H, d, J=7.5 Hz, 1‴-H), 4.56 (1H, d, J=7.5 Hz, 1″-H), 4.58 (1H, d, J=10.6 Hz, 6-H), 6.81 (1H, s, $CH(Ph)_2$), 6.82 (1H, s, $CH(Ph)_2$), 6.92 (1H, d, J=2.9 Hz, 10-H), 7.12~7.20 (5H, Ar-H), 7.31 (1H, d, J=2.9 Hz, 12-H), 7.33~7.46 (6H, 4-H and Ar-H), 7.78 (1H, s, 7-H), 8.91 (1H, d, J=7.0 Hz, NH), 12.90 (1H, s, 9-OH) and 13.21 (1H, s, 14-OH).

1-*O*-Diphenylmethyl-9-*O*-*p*-toluenesulfonylbenanomicin A Diphenylmethyl Ester (**7**)

To a solution of **6** (70 mg) in dry acetone (10 ml) were added *p*-toluenesulfonyl chloride (23 mg) and anhydr potassium carbonate (58 mg). The resulting mixture was refluxed for 12 hours and poured into 5% aq solution of citric acid (20 ml). After removal of acetone under reduced pressure the aq solution was extracted by EtOAc (20 ml). The organic layer was successively washed with a satd $NaHCO_3$ solution, 5% citric acid solution and satd NaCl solution and concentrated. The resulting solid was purified on a preparative TLC plate ($CHCl_3$/MeOH/water 100:15:1.5) to afford **7** (39 mg, 50%). FAB-MS (negative) *m/z* 1313 (M^-). ^{1}H NMR δ 1.03 (3H, d, J=7.3 Hz, 3′-H), 1.21 (3H, d, J=6.3 Hz, 6″-H), 2.20 (3H, s, $SO_2C_6H_4CH_3$), 2.24 (3H, s, 16-H), 3.98 (3H, s, 11-OCH_3), 4.39 (1H, q, J=7.3 Hz, 2′-H), 4.40 (1H, d, J=7.3 Hz, 1‴-H), 6.92 (1H, d, J=2.4 Hz, 10-H), 7.28 (1H, d, J=2.4 Hz, 12-H), 8.03 (1H, s, 7-H), 8.98 (1H, d, J=7.3 Hz, NH) and 12.61 (1H, s, 14-OH).

9-Deoxybenanomicin A (**3**)

To a solution of tosylate **7** (84 mg) in MeOH (5 ml) and $CHCl_3$ (5 ml) was added $NiCl_2 \cdot 6H_2O$ (91 mg) at room temperature. The resulting mixture was stirred for 1 hour at that temperature, then cooled to −78°C. To this mixture was added sodium borohydride (280 mg) in one portion. The mixture was stirred for 3 hours at room temperature, poured into an 5% aq solution of citric acid and extracted with $CHCl_3$. The organic layer was washed with $NaHCO_3$ and concentrated under reduced pressure. The resulting solid was hydrolyzed with 2 M NaOH solution (14 ml) in MeOH (7 ml) overnight at room temperature and purified by a silica-gel column chromatography ($CHCl_3$/butanol/pyridine/water 4:3:5:1) to give **3** (14 mg). FAB-MS (negative) *m/z* 811 (M^-). ^{1}H NMR δ 1.12 (3H, d, J=6.3 Hz, 6″-H), 1.34 (3H, d, J=7.3 Hz, 3′-H), 2.32 (3H, s, 16-H), 3.99 (3H, s, 11-OCH_3), 4.51 (1H, d, J=10.2 Hz, 5-H), 4.59 (1H, d, J=10.2 Hz, 6-H), 4.63 (1H, d, J=7.9 Hz, 1″-H), 7.20 (1H, s, 4-H), 7.48 (1H, dd, J=2.6 and 8.6 Hz, 10-H), 7.69 (1H, d, J=2.3 Hz, 12-H), 8.06 (1H, s, 7-H), 8.19 (1H, d, J=8.6 Hz, 9-H) and 8.38 (1H, d, J=7.3 Hz, NH). ^{13}C NMR δ 16.2 (C-6″), 16.8 (C-3′), 19.0 (C-16), 47.5 ((C-2′), 56.0 (11-OCH_3), 65.5 (C-5‴), 69.3, 70.0, 70.3 (C-4″, 2″, 5″, 4‴), 71.8 (C-6), 73.6 (C-2‴), 75.9 (C-3‴), 81.5 (C-5), 82.9 (C-3″), 104.3 (C-1″), 105.1 (C-1‴), 126.4 (C-2), 129.5 (C-9), 131.4, 134.6 (C-7a, 12a), 137.1 (C-3), 137.9 (C-4a), 147.6 (C-6a), 150.9 (C-1), 156.3 (C-14), 164.0 (C-11), 166.8 (C-15), 173.8 (C-1′), 180. 1 (C-8) and

188.3 (C-13). Benanomicin A (16 mg), derived from simply de-*O*-tosylated **6** during hydride reduction, was also isolated.

9-*O*-Methylbenanomicin A (**4**)

To a solution of **6** (110 mg) in anhydr DMF (4 ml) were added 60% oily NaH (8 mg) and iodomethane (16 μl) at room temperature under an argon atmosphere. The solution was stirred overnight and NH_4Cl (11 mg) was added to this solution. The mixture was diluted with EtOAc (10 ml), successively washed with a satd $NaHCO_3$ solution, 5% citric acid solution and satd NaCl solution and concentrated. The resulting solid was hydrolyzed with 2 M NaOH solution (2 ml) in MeOH (2 ml) at room temperature for 6 hours. The solution was poured into water (adjusted to pH 2 by 1 M HCl, 50 ml) and the resulting precipitate was collected by centrifugation and purified by a silica-gel column chromatography ($CHCl_3$/butanol/pyridine/water 50:20:20:2) to afford 1-*O*-diphenylmethyl-9-*O*-methyl derivative **9** (36 mg, 38%). This compound was hydrogenolyzed in EtOH with 10% Pd on carbon overnight and purified on Cosmosil® 75 C_{18} resin to give **4** (14 mg, 48%). FAB-MS (negative) *m/z* 841 (M^-). ^1H NMR δ 1.12 (3H, d, J=6.3 Hz, 6″-H), 1.34 (3H, d, J=7.3 Hz, 3′-H), 2.32 (3H, s, 16-H), 3.96 and 4.00 (each 3H, s, 9-OCH_3 and 11-OCH_3), 7.07 (1H, d, J=2.3 Hz, 10-H), 7.19 (1H, s, 4-H), 7.40 (1H, d, J=2.3 Hz, 12-H), 7.99 (1H, s, 7-H), 8.38 (1H, J=6.9 Hz, NH) and 13.80 (1H, 14-OH). ^{13}C NMR δ 16.2 (C-6″), 16.8 (C-3′), 20.2 (C-16), 47.5 ((C-2′), 56.0 and 56.5 (9-OCH_3 and 11-OCH_3), 65.5 (C-5‴), 69.3~70.3 (C-4″, 2″, 5″, 4‴), 72.7 (C-6), 73.6 (C-2‴), 75.9 (C-3‴), 81.6 (C-5), 83.1 (C-3″), 113.7 (C-14b), 114.8 (C-13a), 115.0 (C-7), 127.5 (C-2), 133.1 (C-7a), 136.1 (C-12a), 137.1 (C-3), 137.8 (C-4a), 147.4 (C-6a), 150.7 (C-1), 155.6 (C-14), 162.5 (C-9), 164.4 (C-11), 166.7 (C-15), 173.8 (C-1'), 178.4 (C-8) and 188.3 (C-13).

14-*O*-Methylbenanomicin A (**5**)

To a solution of **6** (200 mg) in MeOH (1 ml) and acetonitrile (9 ml) were added *N*,*N*-diisopropylethylamine (70 μl) and diazotrimethylsilylmethane (260 μl of a 10% hexane solution) at room temperature. The solution was stirred overnight and concentrated under reduced pressure. The residue was dissolved in EtOAc (30 ml), successively washed with a satd $NaHCO_3$ solution, 5% citric acid solution and satd NaCl solution and concentrated. The resulting solid was purified by a silica-gel column chromatography ($CHCl_3$/MeOH 5:1) to afford **10** (176 mg, 87%). Compound **10** (160 mg) was dissolved in MeOH (5 ml) and 2 M NaOH solution (5 ml). The solution was stirred at room temperature overnight and acidified to pH 2 with 1 M HCl solution. The resulting solid was centrifuged and washed with water. The solid was hydrogenolyzed in EtOH with Pd-black overnight and purified on Cosmosil® 75 C_{18} resin to give **5** (38 mg, 33%). FAB-MS *m/z* 842 ($[M+H]^+$) and 843 ($[M+2H]^+$). ^1H NMR δ 1.11 (3H, d, J=6.3 Hz, 6″-H), 1.34 (3H, d, J=7.4 Hz, 3′-H), 2.34 (3H, s, 16-H), 3.68 (3H, s, 14-OCH_3), 3.94 (3H, s, 11-OCH_3), 4.58 (1H, d, J=10.0 Hz, 5-H), 4.62 (1H, d, J=10.0 Hz, 6-H), 6.84 (1H, d, J=2.3 Hz, 10-H), 7.20 (1H, d, J=2.3 Hz, 12-H), 7.23 (1H, s, 4-H), 8.33 (1H, s, 7-H), 8.40 (1H, NH) and 12.68 (1H, 9-OH). ^{13}C NMR δ 16.1 (C-6″), 16.8 (C-3′), 18.9 (C-16), 47.5 (C-2′), 56.1 (11-OCH_3), 62.2 (14-OCH_3), 65.4 (C-5‴), 69.3 (C-4‴), 69.9 (C-2″), 70.1 (C-5″), 70.3 (C-4‴), 71.5 (C-6), 73.5 (C-2‴), 75.9 (C-3‴), 81.3 (C-5), 82.8 (C-3″), 104.2 (C-1″), 105.0 (C-1‴), 105.5 (C-10), 106.9 (C-12), 109.7 (C-8a), 114.0 (C-14b), 119.3 (C-4, 7), 125.0 (C-13a), 127.6 (C-2), 131.1 (C-14a), 133.4 (C-7a), 136.1 (C-12a), 137.5 (C-3), 138.1 (C-4a), 145.9 (C-6a), 150.7 (C-1), 154.7 (C-14), 163.9 (C-9), 166.0 (C-11), 166.5 (C-15), 173.6 (C-1′), 180.1 (C-13) and 185.2 (C-8).

Antifungal Activity

MIC on glucose-nutrient agar was determined by the 2-fold agar dilution method after incubation at 27°C for 42 hours.

Binding Assay to *Saccharomyces* Cells

Binding of compounds to *Saccharomyces cerevisiae* X21810-1A cells (2×10^7 cells) and recovery from the cells were performed by the method in the literature[11]. The DMSO-extract was subjected to HPLC analysis to determine the amount of cell-bound samples under the following conditions: Column, Inertsil® $_5C_{18}$ (4.6×250 mm); mobile phase, AcOH/CH_3CN/H_2O 1:6:11; flow rate, 1 ml/minute; detection, UV at 280 nm.

Benanomicin A (**1**), 21.3 μg/10^7 cells; 9-deoxybenanomicin A (**3**), 13.6 μg/10^7 cells; 9-*O*-methylbenanomicin A (**4**), 3.3 μg/10^7 cells; 14-*O*-methylbenanomicin A (**5**), not detected.

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