# A Synthetic Approach to Benanomicin A

## 1. Synthesis of 5,6-Dihydrobenzo[*a*]naphthacenequinone

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(Received for publication April 22, 1997)

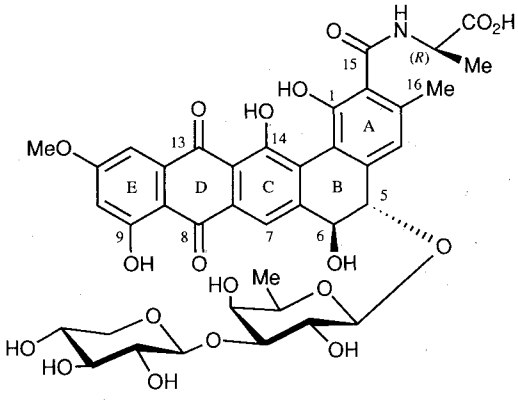
5,6-Dihydrobenzo[*a*]naphthacenequinone has been constructed by DIELS-ALDER reaction of an outer-ring diene with a naphthoquinone regioselectively. Similarly, the 14-hydroxy-5,6-dihydrobenzo[*a*]naphthacenequinone (**13**) has also been synthesized *via* the reaction of vinylketene acetal (**11**) with naphthoquinone.

Members of the family of naturally occurring benzo[*a*]naphthacenequinones[1~8] show various kinds of biological activity. Among them, benanomicin A (**1**)[9,10], isolated from the culture broth of *Actinomadura spadix* MH193-16F4, is one of the most important compounds because it exhibits significant antifungal and anti-HIV activity[11~13]. Although a few synthetic studies on benzo[*a*]naphthacenequinone pigments G-2N and G-2A were reported[14,15], benanomicinones have not been synthesized to date. We are interested in investigating the structure-activity relationships of benanomicins[16], so it is important to develop a synthetic route not only to **1**, but also to analogs with improved biological activity. For this purpose, we started a program directed toward the general construction of the substituted 5,6-dihydrobenzo[*a*]naphthacenequinone skeleton, *i.e.* benanomicinone and analogs.

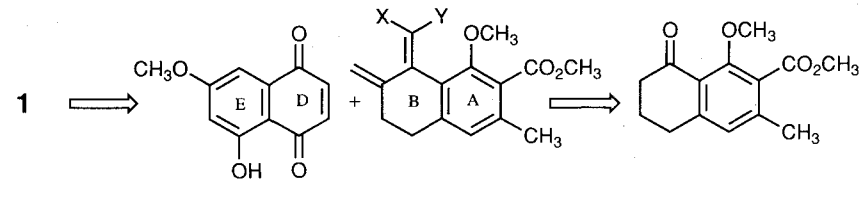
The synthetic strategy for the 5,6-dihydrobenzo[*a*]-naphthacenequinone derivative is outlined retrosynthetically in Scheme 1. It involves DIELS-ALDER reaction of an outer-ring diene A-B ring system, with a naphthoquinone D-E ring.

First, we attempted to construct the unsubstituted 5,6-dihydrobenzo[*a*]naphthacenequinone skeleton **8**, starting from a commercially available unsubstituted α-tetralone (**2**) (Scheme 2). Heating **2** with paraformaldehyde and dimethylamine hydrochloride in ethanol gave the keto-amine (**3**) in 86% yield[17]. WITTIG olefination of **3** with (methoxymethylene)phosphorane, generated *in situ via* phenyllithium and (methoxymethyl)triphenylphosphonium chloride at −45°C in tetrahydrofuran, at 0°C afforded a 6 : 1 mixture of the enol methyl ethers (**4**) in 72% yield. The ratio of isomers was determined by $^1$H NMR integration of the olefin proton signals ($\delta$ 6.57 for major isomer and $\delta$ 6.15 for minor one). It was difficult to separate the isomers completely because they

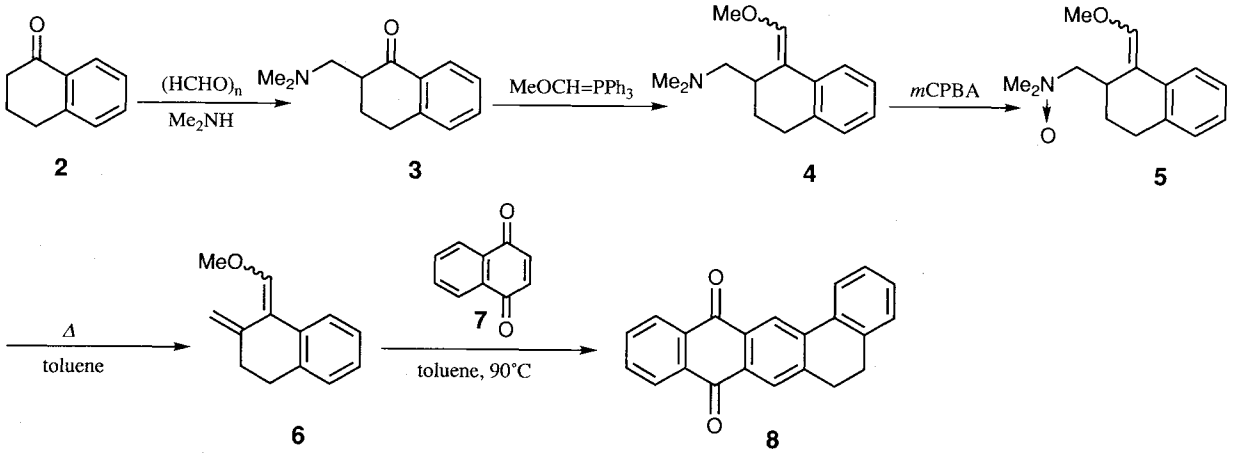
Fig. 1. Structure of benanomicin A (**1**).



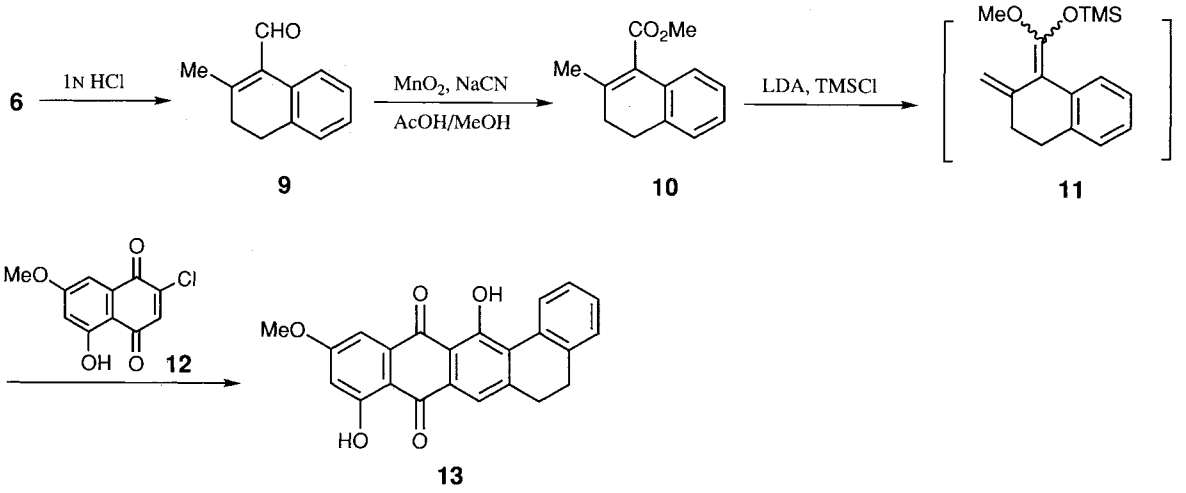

Scheme 1. Retrosynthetic analysis of benanomicinone.



Scheme 2. Synthesis of the unsubstituted 5,6-dihydrobenzo[*a*]naphthacenequinone (**8**).




Scheme 3. Synthesis of the A-ring unsubstituted 14-hydroxy-5,6-dihydrobenzo[*a*]naphthacenequinone (**13**).




had similar Rf values and partially decomposed to the corresponding aldehyde during contact with silica-gel. Treatment of **4** with 1 equiv of *m*-chloroperbenzoic acid in chloroform at 0°C gave the *N*-oxide (**5**). Heating **5** in toluene gave the diene (**6**), which was easily cyclized with 1,4-naphthoquinone (**7**) in toluene at 90°C to afford the unsubstituted 5,6-dihydrobenzo[*a*]naphthacenequinone (**8**) in 38% yield from **5**. The spectral data (NMR, HR-MS and UV) of **8** strongly supported the 5,6-dihydrobenzo[*a*]naphthacenequinone structure. Oxidation of **8** with trimethylamine *N*-oxide in DMF afforded the known aromatic benzo[*a*]naphthacenequinone[18].

The next stage was to synthesize 14-hydroxy-5,6-dihydrobenzo[*a*]naphthacenequinone (Scheme 3). For this purpose, compound **6** was converted to the vinylketene acetal (**11**) *via* α,β-unsaturated ester (**10**). Treatment of the α,β-unsaturated aldehyde (**9**), obtained upon treatment of **6** with 1 M hydrochloric acid, with a mixture of sodium cyanide, activated manganese dioxide and glacial acetic acid in methanol[19] gave the corresponding methyl ester (**10**) in 30% yield. Reaction of **10** with lithium diisopropylamide and chlorotrimethylsilane at −78°C, cyclization of the resulting **11** with 2-chloro-5-hydroxy-7-methoxynaphthoquinone (**12**)[20] at room temperature, followed by slow percolation of the crude adduct through a column of silica-gel gave the desired product (**13**) (9-OH at δ 12.98 and 14-OH at δ 13.88) in 72% yield based on the recovered starting material (Scheme 3). The structure of **13** was entirely confirmed by the HMBC correlations between 7-H (δ 7.75) and C-8 (δ 186.2), and 12-H (δ 7.43) and C-13 (δ 188.1). As expected, the DIELS-ALDER reaction proceeded regio-

selectively, and no regioisomeric product was detected.

We have successfully developed a general and flexible synthetic route to A-ring unsubstituted benzo[*a*]-naphthacenequinones. Obviously, it can also be applied to the synthesis of highly substituted benzo[*a*]naphthacenequinones. This is our next subject.

## Experimental

### General

Mass spectra (EI-MS) were measured on a Hitachi M80H mass spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Jeol JNM-GX400 spectrometer. UV spectra were recorded on a Hitachi U-3210 spectrometer. Melting points were determined on a Yanagimoto micro melting point apparatus.

### 2-(Dimethylamino)methyl-1-oxo-1,2,3,4-tetrahydronaphthalene (3)

A mixture of α-tetralone (**2**) (3.85 g, 26.4 mmol), dimethylammonium chloride (2.82 g, 34.6 mmol), paraformaldehyde (1.08 g, 12 mmol) and 3 drops of conc HCl in 95% EtOH 40 ml was heated at 90°C for 24 hours. After evaporation, the residue was partitioned between diethyl ether and 1 M HCl under cooling. The aq layer was adjusted to pH 9 with satd $NaHCO_3$ solution, saturated with NaCl and extracted with chloroform. After evaporation, compound **3** (4.6 g) was obtained. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.87~2.03 (1H, m, one of 3-H), 2.28 (6H, s, $N(CH_3)_2$), 2.39 (1H, m, one of 3-H), 2.52 (1H, dd, $J$=11.9, 8.9 Hz, one of $CH_2N(CH_3)_2$), 2.69 (1H, m, 2-H), 2.79 (1H, dd, $J$=11.9, 4.6 Hz, one of $CH_2N(CH_3)_2$), 3.01 (2H, m, 4-$H_2$), 7.23~7.34 (2H, m, 2×Ar-H), 7.47 (1H, ddd, $J$=7.8, 7.3, 1.5 Hz, Ar-H), 8.02 (1H, dd, $J$=7.8, 1.5 Hz, Ar-H).

### 2-(Dimethylamino)methyl-1-methoxymethylene-1,2,3,4-tetrahydronaphthalene (4)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (11 g, 32 mmol) in anhydr THF (80 ml) was added 1.8 M phenyllithium in cyclohexane-diethyl ether solution (15.6 ml, 28 mmol) at −45°C. After stirring at the same temperature for 30 minutes, compound **3** (2.03 g, 10 mmol) in anhydr THF (20 ml) was added and then stirred at 0°C for 15 hours. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed with satd NaCl solution, dried over anhydr $Na_2SO_4$ and evaporated. The residue was dissolved in diethyl ether, washed with $H_2O$ and then extracted with 1 M HCl under cooling. The aq layer was adjusted to pH 9 with satd $NaHCO_3$ solution, saturated with NaCl and extracted with chloroform. After evaporation, the residue was chromatographed on silica-gel with chloroform~chloroform - MeOH (19 : 1) to give **4** (1.66 g). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.23 and 2.26 (each 3H, s, $N(CH_3)_2$), 3.74 (3H, s, $OCH_3$), 6.15 (1/7H, s, enolic olefin H), 6.57 (6/7H, s, enolic olefin H), 7.34 (6/7H, m, Ar-H), 8.08 (1/7H, d, $J$=7.9 Hz, Ar-H).

### 2-(Dimethylamino)methyl-1-methoxymethylene-1,2,3,4-tetrahydronaphthalene *N*-Oxide (5)

A solution of *m*CPBA (480 mg, 2.78 mmol) in chloroform (4 ml) was added to a solution of compound **4** (641 mg, 2.78 mmol) in chloroform (3 ml) at 0°C. After stirring at the same temperature for 1 hour, the reaction mixture was passed through a column of basic alumina (pH 10) with chloroform~chloroform - MeOH (19 : 1) to afford **5** (604 mg). FAB-MS $m/z$ 248 ($[M+H]^+$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.14 and 3.27 (each 18/7H, s, $N(CH_3)_2$), 3.20 and 3.23 (each 3/7H, s, $N(CH_3)_2$), 3.74 (3/7H, s, $OCH_3$), 3.77 (18/7H, s, $OCH_3$), 6.40 (1/7H, s, enolic olefin H), 6.47 (6/7H, s, enolic olefin H), 7.88 (1/7H, dd, $J$=6.6, 2 Hz, Ar-H).

### 5,6-Dihydrobenzo[*a*]naphthacene-8,13-dione (8)

A solution of compound **5** (24.7 mg, 0.1 mmol) in anhydr toluene (1.5 ml) was heated at 90°C for 15 minutes. After evaporation, 1-methoxymethylene-2-methylene-1,2,3,4-tetrahydronaphthalene (**6**) was obtained. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.83 (3/7H, s, $OCH_3$), 3.87 (18/7H, s, $OCH_3$), 4.62 and 4.98 (each 1/7H, bs, olefin H), 5.23 and 5.79 (each 6/7H, bs, olefin H), 6.56 (1/7H, s, enolic olefin H), 6.71 (6/7H, s, enolic olefin H). A mixture of **6** and 1,4-naphthoquinone (**7**) (16 mg, 0.1 mmol) in toluene (2 ml) was heated at 90°C for 8 hours. After evaporation, the residue was chromatographed on silica-gel with chloroform - hexane (1 : 2) to give **8** (12 mg). MP 243°C. EI-MS $m/z$ 310 ($M^+$). HREI-MS Found: $m/z$ 310.0984 ($M^+$), Calcd for $C_{22}H_{14}O_2$: 310.0992. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.96 and 3.07 (each 2H, m, 5- and 6-$H_2$), 7.29~7.41 (3H, m, 3×Ar-H), 7.78~7.84 (2H, m, 2×Ar-H), 7.93 (1H, dd, $J$=8.9, 1.7 Hz, Ar-H), 8.17 (1H, s, 7-H), 8.31~8.36 (2H, m, 2×Ar-H), 8.67 (1H, s, 14-H). UV $\lambda_{max}^{MeOH}$ nm (ε) 244 (28,700), 289 (47,300), 327 (sh, 8,300), 371 (6,700).

### Benzo[*a*]naphthacene-8-13-dione

A solution of **8** (412 mg) and trimethylamine *N*-oxide dihydrate (1.48 g) in DMF (100 ml) was heated at 100°C

for 24 hours. After cooling to room temperature we obtained yellow needles (410 mg) from the solution. MP 288°C (lit[18], 280°C). UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) 230 (26,600), 235 (sh, 26,500), 265 (sh, 32,900), 272 (36,200), 298 (sh, 18,500), 324 (sh, 19,100), 405 (4,500).

1-Formyl-2-methyl-3,4-dihydronaphthalene (**9**)

To a solution of **6** (186 mg, 1 mmol) in dioxane (2 ml) was added 1 M HCl (0.2 ml) at room temperature. After 30 minutes, the reaction mixture was extracted with chloroform. The chloroform layer was washed with $H_2O$, satd NaCl solution, dried over anhydr $Na_2SO_4$ and evaporated to give **9** (141 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.39 (3H, s, $CH_3$), 2.45 (2H, m, 3-$H_2$), 2.75 (2H, m, 4-$H_2$), 7.14~7.25 (3H, m, 3 × Ar-H), 7.91 (1H, d, $J$=7.3 Hz, Ar-H), 10.40 (1H, s, CHO).

Methyl 2-Methyl-3,4-dihydro-1-naphthalenecarboxylate (**10**)

To a mixture of activated manganese dioxide (201 mg, 2.31 mmol), sodium cyanide (30 mg, 0.61 mmol) and glacial acetic acid (10.5 mg, 0.17 mmol) in MeOH (2 ml) was added a solution of **9** (30 mg, 0.17 mmol) in MeOH (1 ml). After stirring at room temperature for 3 hours, the insoluble material was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform, washed with $H_2O$ and satd NaCl solution, and dried over anhydr $Na_2SO_4$. After removal of the solvent, the residue was chromatographed on silica-gel with chloroform-hexane (1:1) to give **10** (11 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.01 (3H, s, $CH_3$), 2.32 (2H, m, 3-$H_2$), 2.80 (2H, m, 4-$H_2$), 3.88 (3H, s, $CO_2CH_3$), 7.05 (1H, d, $J$=6.8 Hz, Ar-H), 7.07~7.18 (3H, m, 3× Ar-H)

9,14-Dihydroxy-11-methoxy-5,6-dihydrobenzo[*a*]naphthacene-8,13-dione (**13**)

To a solution of **10** (10 mg, 0.05 mmol) in anhydr THF (0.5 ml) was added a 2.0 M LDA solution (35 $\mu$l, 0.07 mmol) at −78°C. The stirring was maintained at −78°C for 30 minutes and then a solution of chlorotrimethylsilane (11 mg, 0.1 mmol) in anhydr THF (0.2 ml) was added. After stirring at room temperature for 1 hour, a solution of 2-chloro-5-hydroxy-7-methoxy-1,4-naphthoquinone (**12**) (12 mg, 0.05 mmol) in anhydr THF (0.5 ml) was added. The reaction mixture was stirred for 15 hours. After evaporation, the residue was chromatographed on silica-gel with chloroform-hexane (1:1) to give **13** (1.5 mg). MP 237~239°C. EI-MS $m/z$ 372 ($M^+$). HREI-MS Found: $m/z$ 372.1000 ($M^+$), Calcd for $C_{23}H_{16}O_5$: 372.0997. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.87 and 2.95 (each 2H, m, 5- and 6-$H_2$), 3.95 (3H, s, $OCH_3$), 6.72 (1H, d, $J$=2.4 Hz, 10-H), 7.30~7.33 (2H, m, 3- and 4-H), 7.37 (1H, ddd, $J$=7.8, 7.4, 2.0 Hz, 2-H), 7.43 (1H, d, $J$=2.4 Hz, 12-H), 7.75 (1H, s, 7-H), 8.58 (1H, d, $J$=7.8 Hz, 1-H), 12.98 (1H, s, 9-OH), 13.88 (1H, s, 14-OH). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 28.6 (C-5), 30.8 (C-6), 56.1 (11-$OCH_3$), 106.8 (C-10), 107.9 (C-12), 110.8 (C-8a), 115.2 (C-13a), 119.3 (C-7), 126.7 (C-2), 127.7 (C-4), 128.7 (C-3), 129.1 (C-1), 129.5 (C-14a), 130.8 (C-14b), 131.3 (C-7a), 135.0 (C-12a), 138.4 (C-4a), 148.8 (C-6a), 161.2 (C-14), 165.5 (C-9), 166.3 (C-11), 185.9 (C-8), 188.1 (C-13). UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) 232 (sh, 11,400), 266 (sh, 9,800), 274 (sh, 10,500), 288 (11,900), 302 (sh, 10,800), 334 (sh, 2,900), 454 (5,100).

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