# A Synthetic Approach to Benanomicin A: Synthesis of the Substituted 5,6-Dihydrobenzo[*a*]naphthacenequinone

Sehei Hirosawa,† Toshio Nishizuka, Shinichi Kondo, and Daishiro Ikeda*
*Institute of Microbial Chemistry, M. C. R. F., 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141*

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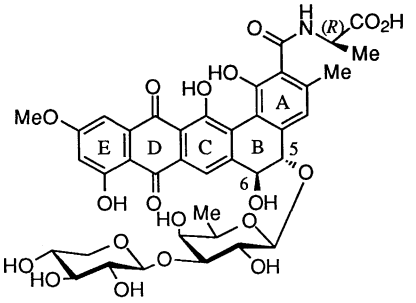
Tri-substituted α-tetralone has been synthesized and applied to the general synthesis of the substituted 5,6-dihydrobenzo[*a*]-naphthacenequinone.

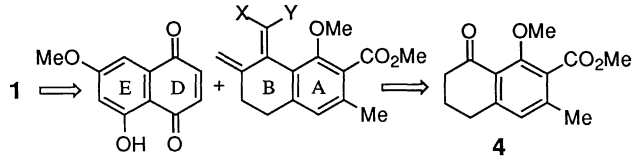
Benanomicin A (**1**),[1, 2] isolated from the culture broth of *Actinomadura spadix* MH 193-16F4, exhibits the antifungal and



Benanomicin A (**1**)

anti-HIV activity.[3-5] Investigation of the structure-activity relationships of benanomicins[6] led us to start a program directed toward the general construction of the substituted 5,6-dihydrobenzo[*a*]naphthacenequinone skeleton,[7] *i.e.* benanomicinone and the analogs.

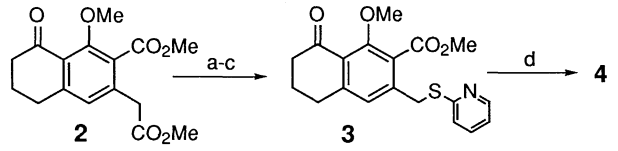
The synthetic strategy to the 5,6-dihydrobenzo[*a*]naphthacenequinone derivative is outlined retrosynthetically in Scheme 1.



**Scheme 1.**

It involves Diels-Alder reaction of an outer-ring diene, A-B ring with a naphthoquinone, D-E ring. The A-B ring system is derived from the tri-substituted α-tetralone (**4**) which is a key intermediate to benanomicinone.

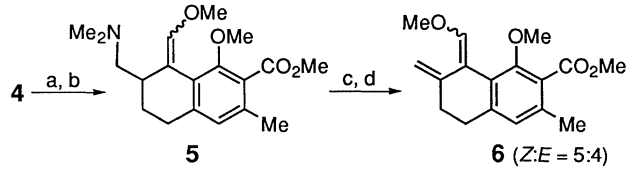
The starting diester **2**, readily prepared by Yamaguchi's procedure,[8] was converted to the synthetically important inter-



a) NaOH, aq MeOH, 60 °C; b) $(COCl)_2$, toluene, r. t.; c) 2-mercapto-pyridine *N*-oxide Na salt, toluene, reflux (79% from **2**); d) $Ni_2B$, $H_3BO_3$, aq EtOH, 80 °C (95%).

**Scheme 2.**

mediate **4** in a good yield by using Barton's method[9] without DMAP (Scheme 2). Namely, the selective hydrolysis of an aliphatic ester of **2** with 2 M aqueous methanolic NaOH at 60 °C gave a mono-acid. When the acid chloride obtained upon treatment of the mono-acid with oxalyl chloride was heated with 2-mercaptopyridine *N*-oxide sodium salt, the decarboxylative rearrangement occurred to give the pyridyl sulfide **3**. The rearrangement in the presence of DMAP also provided **3**, but the yield was less than 10%. The reductive desulfurization of **3** with nickel boride afforded the desired tri-substituted α-tetralone **4**[10] in 75% yield from **2**. The one-pot direct radical decarboxylation of the mono-acid (2-mercaptopyridine *N*-oxide, DCC, DMAP/$Bu_3SnH$)[9] failed.



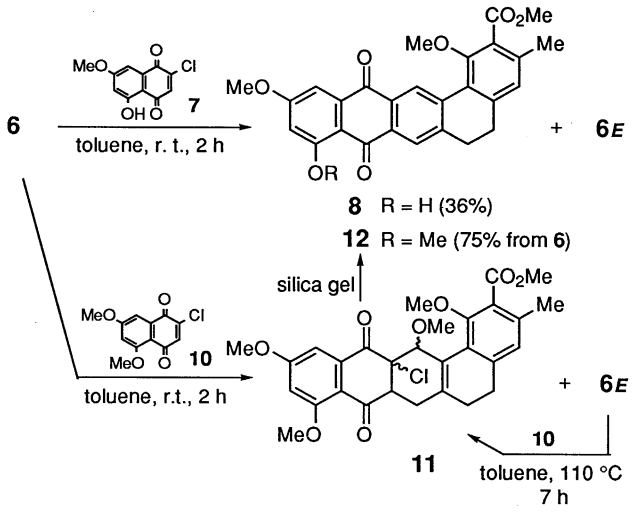
a) $(HCHO)_n$, $Me_2NH$-HCl, HCl (cat.), 95% EtOH, 90 °C (86%); b) $Ph_3P{=}CHOCH_3$, THF, –45 °C~ 0 °C ~ r. t. (35%); c) mCPBA, $CH_2Cl_2$, 0 °C (92%); d) toluene, 90 °C (100%).

**Scheme 3.**

α-Tetralone **4** was converted to the methoxy-diene **6** in four steps operation (Scheme 3). Mannich reaction of **4**, followed by Wittig reaction with methoxymethylenephosphorane afforded a *Z*/*E* mixture (approximately 5:4 ratio) of the enol methyl ethers **5** in 35% yield.[11] It was difficult to separate the isomers completely because they had similar Rf values and partially decomposed to the corresponding aldehyde during contact with silica gel. Treatment of **5** with mCPBA in dichloromethane, followed by heating in toluene and evaporation gave **6** which was pure enough for the next Diels-Alder reaction without further purification.

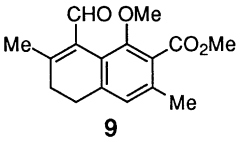
Diels-Alder reaction of **6** (Scheme 4) with 2-chloro-5-hydroxy-7-methoxynaphthoquinone **7**[12] in toluene at r.t. for 2 h followed by a careful work-up afforded the desired product **8**[13] in 36% yield along with the unreacted minor *E*-diene **6***E*.[13] Extending the reaction time, raising the reaction temperature, or adding Lewis acid did not improve the yield. The aldehyde **9**[13] was obtained instead of **6***E*. The reaction of the recovered **6***E* with **7** was attempted under various conditions. However, only a trace of **8** was detected and **9** was a main product again.

Interestingly, however, when **6** was treated with 2-chloro-5,7-dimethoxynaphthoquinone **10**[12] under the same conditions as described for **8**, the intermediate **11**[13] and **6***E* were obtained. Two compounds were easily separable by trituration with hexane since **6***E* was soluble in hexane. Compound **11** was also obtained from **6***E* by heating with **10** in toluene for 7 h. The initial adduct **11** did not undergo elimination of hydrogen




**Scheme 4.**

chloride and methanol *in situ*, but upon treatment with silica gel **12**[13] was formed in 75% yield from **6**. These results indicated that the hydrogen chloride, liberated from the aromatization of



**9**

Diels-Alder adduct, caused less reactive **6E** to decompose to give **9**. The structures of **8** and **12** were entirely confirmed by the HMBC experiments. As expected, the Diels-Alder reaction proceeded regioselectively, and no regioisomeric product was detected.

We have synthesized the key intermediate **4** and applied to the synthesis of the substituted benzo[*a*]naphthacenequinone skeleton successfully. We believe that **4** will also be able to be as a useful precursor in the synthesis of other members of the naturally occurring benzo[*a*]naphthacenequinone family. Further studies on this approach are currently in progress.

## References and Notes


† Formerly Shyh-Pyng Huang.

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10 **4**: Mp 106 °C. $^1$H NMR ($CDCl_3$): δ 2.07 (2H, m, 3-$H_2$), 2.29 (3H, s, $CH_3$), 2.63 (2H, m, 2-$H_2$), 2.91 (2H, m, 4-$H_2$), 3.84 (3H, s, $OCH_3$), 3.91 (3H, s, $CO_2CH_3$) and 6.87 (1H, s, 5-H). Anal. Found: C, 67.42; H, 6.55%. Calcd for $C_{14}H_{16}O_5$: C, 67.73; H, 6.50%.

11 The ratio of two isomers was determined by $^1$H NMR integration of the olefin proton signals (δ 6.05 for *Z*-isomer and 7.03 for *E*).

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13 **6E**: The *E*-geometry was determined by NOE experiments. FABMS: *m/z* 288 $M^+$. $^1$H NMR ($CDCl_3$): δ 2.23 (3H, s, $CH_3$), 2.44 and 2.60 (each 2H, m, 5 and 6-$H_2$), 3.69 and 3.81 (each 3H, s, 2x$OCH_3$), 3.92 (3H, s, $CO_2CH_3$), 5.23 (1H, d, *J*=1.5 Hz, olefin H), 5.75 (1H, d, *J*=1.5 Hz, olefin H), 6.74 (1H, s, 4-H) and 7.18 (1H, s, enolic olefin H). **8**: FABMS: *m/z* 459 $(M+1)^+$. $^1$H NMR ($CDCl_3$): δ 2.33 (3H, s, $CH_3$), 2.83 and 2.98 (each 2H, m, 5 and 6-$H_2$), 3.65 (3H, s, 1-$OCH_3$), 3.95 (3H, s, 11-$OCH_3$), 3.99 (3H, s, $CO_2CH_3$), 6.71 (1H, d, *J*=2.5 Hz, 10-H), 6.94 (1H, s, 4-H), 7.39 (1H, d, *J*=2.5 Hz, 12-H), 8.14 (1H, s, 7-H), 9.20 (1H, s, 14-H) and 12.95 (1H, s, OH). **9**: $^1$H NMR ($CDCl_3$): δ 2.25 (3H, s, $CH_3$), 2.29 (3H, s, $CH_3$), 2.31 and 2.69 (each 2H, m, 5 and 6-$H_2$), 3.55 (3H, s, $CO_2CH_3$), 3.93 (3H, s, $CO_2CH_3$), 6.85 (1H, s, 4-H) and 9.81 (1H, s, CHO). **11**: FABMS: *m/z* 541 $(M+1)^+$. $^1$H NMR ($CDCl_3$): δ 2.78 (3H, s, $OCH_3$) and 5.36 (1H, s, 14-H). **12**: FABMS: *m/z* 473 $(M+1)^+$. $^1$H NMR ($CDCl_3$): δ 2.33 (3H, s, $CH_3$), 2.83 and 2.96 (each 2H, m, 5 and 6-$H_2$), 3.65 (3H, s, 1-$OCH_3$), 3.99 (6H, s, 11-$OCH_3$ and $CO_2CH_3$), 4.02 (3H, s, 9-$OCH_3$), 6.79 (1H, d, *J*=2.4 Hz, 10-H), 6.93 (1H, s, 4-H), 7.49 (1H, d, *J*=2.4 Hz, 12-H), 8.10 (1H, s, 7-H) and 9.15 (1H, s, 14-H).