A Synthetic Approach to Benanomicin A

2. Synthesis of the Substituted 5,6-Dihydrobenzo[*a*]naphthacenequinone

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The key intermediate tri-substituted α-tetralone (**8**) has been synthesized, either *via* tandem MICHAEL addition-DIECKMANN condensation reaction between dienolate and methyl crotonate in a low yield or *via* BARTON's radical decarboxylation of diester (**9**) without 4-dimethylaminopyridine in 75% yield, and applied to the synthesis of the substituted 5,6-dihydrobenzo[*a*]naphthacenequinone.

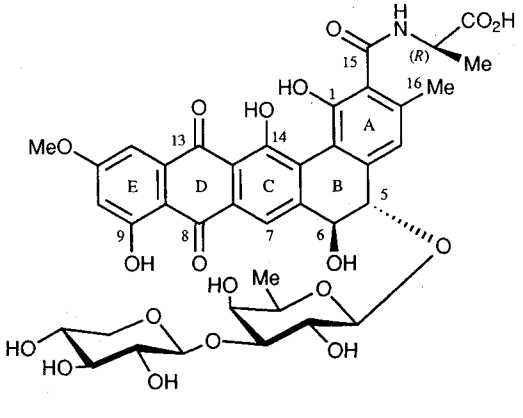
Benanomicin A (**1**)[1,2], isolated from the culture broth of *Actinomadura spadix* MH193-16F4 in 1988, showed antifungal and anti-HIV activity[3~5]. Its unique structure and significant biological activity led us to investigate the structure-activity relationships of benanomicins[6] and start a program directed toward the synthesis of benanomicinone and its analogs.

We disclosed a general and flexible synthetic route to A-ring unsubstituted 5,6-dihydrobenzo[*a*]naphthacenequinones by employing the DIELS-ALDER reaction of an outer-ring diene with a naphthoquinone in a preceding paper[7]. We now report the synthesis of the key intermediate tri-substituted α-tetralone (**8**) and the construction of the substituted 5,6-dihydrobenzo[*a*]naphthacenequinone[8] following the synthetic route previously developed[7]. The choice of **8** as starting compound is based on the following considerations: (1) the A-ring has three suitable functional groups in the right orientations; (2) the B-ring can easily be converted to various outer-ring dienes from which not only benanomicinone and its analogs but other members of the naturally occurring benzo[*a*]naphthacenequinone family can be synthesized.

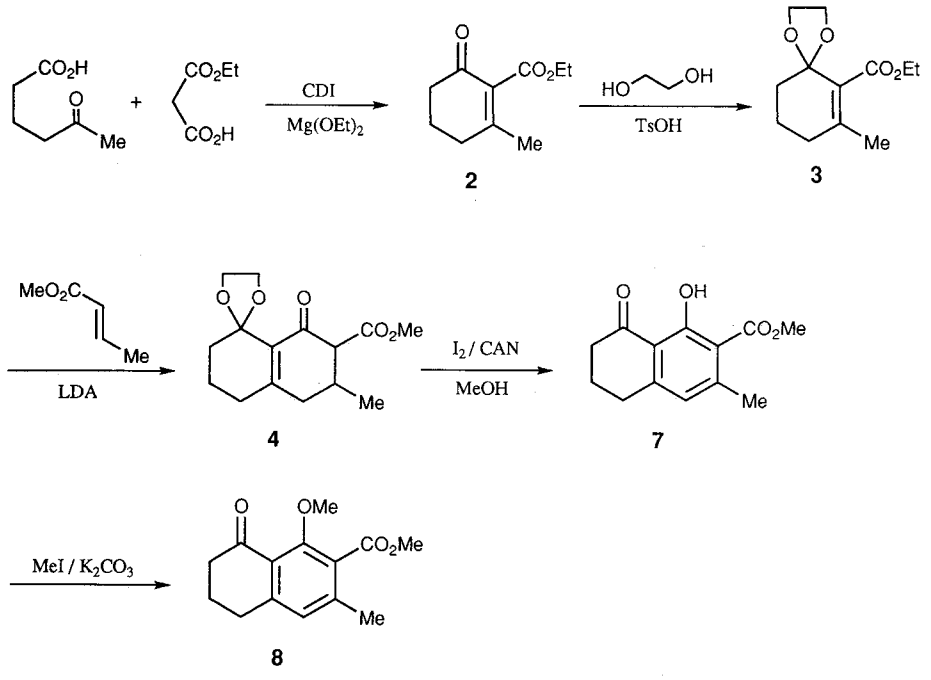
Preparation of the Requisite α-Tetralone Derivative (**8**)

Two different methods were studied. In the first method, α-tetralone (**8**) was synthesized *via* a tandem MICHAEL addition-DIECKMANN condensation reaction between a dienolate and methyl crotonate (Scheme 1). Namely, acetalization of **2** which was prepared from acetobutyric acid and monoethyl malonate according to MASAMUNE's procedure[9] in 80% yield, followed by treatment with 3.5 equiv of lithium diisopropylamide (LDA) and then with excess methyl crotonate in THF to afford the bicyclic β-keto ester (**4**) along with two by-products **5** and **6** in 30%, 25% and 15% respectively. When the reaction was carried out by using one equivalent of LDA about 65% of **3** was recovered and the ratios of **4**, **5** and **6** did not change. Those results revealed that the deprotonation occurred on the exocyclic methyl group and the acetal might be opened by β-elimination from the ester enolate (**a**), followed by re-deprotonation of the resulting β-alkoxy-α,β-unsaturated ester (**b**) to give **c** as shown in Scheme 2. The resulting lithium dienolates (**a** and **c**) were underwent tandem MICHAEL addition-DIECKMANN condensation with methyl crotonate to form **4** and **6**. The oxidative aromatization of **4** was carried out under reflux with iodine-cerium (IV) ammonium nitrate in methanol[10] in the presence of 4A-molecular sieves to afford phenol derivative (**7**) in 20% yield. No trace of the methyl aryl ether (**8**) could be detected. This aromatization was also attempted under various conditions (*N*,*N*′-dicyclohexylcarbodiimide, palladium on activated carbon, *etc.*) without success.

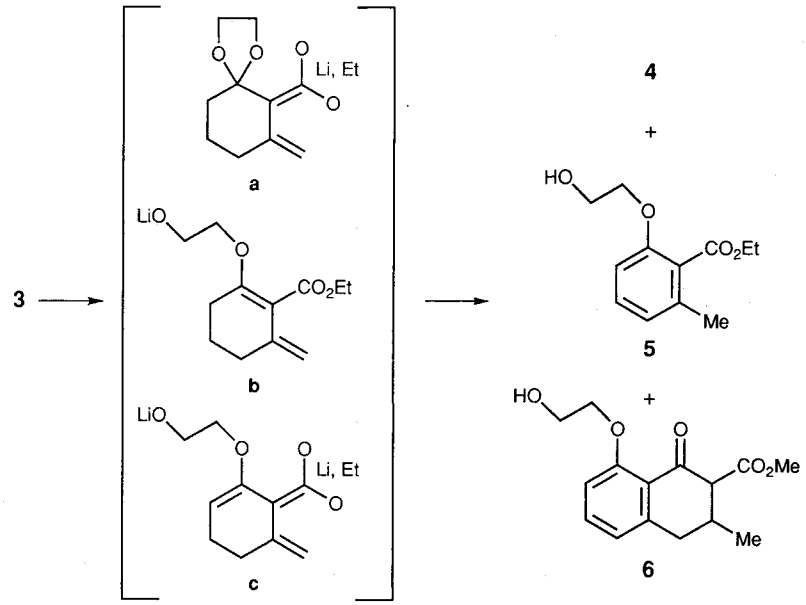
Fig. 1. Structure of benanomicin A (**1**).



Scheme 1. Preparation of the tri-substituted α-tetralone (**8**) by tandem MICHAEL addition-DIECKMANN condensation.

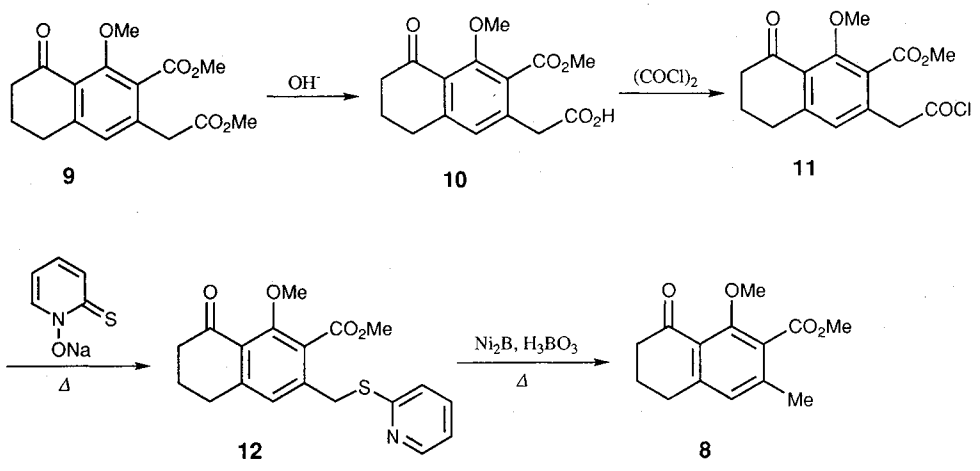


Scheme 2. Mechanism of the formation of **4**, **5** and **6**.

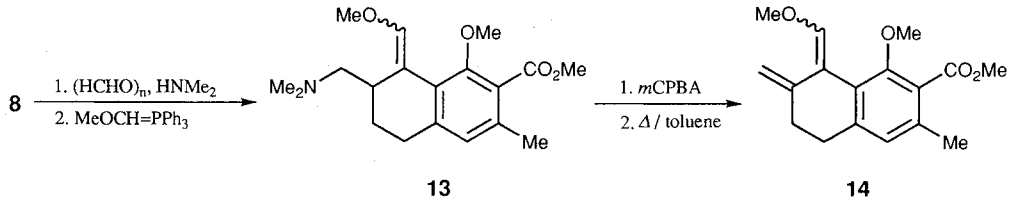


Treating **7** with methyl iodide and potassium carbonate afforded **8** in a good yield. However, this sequence did not provide **8** in a satisfactory yield overall. So, another efficient method as shown in Scheme 3 was explored. It involves the conversion of the diester (**9**) to **8** by using a modified BARTON's decarboxylation[11]. Namely, the selective hydrolysis of aliphatic ester of **9**, readily prepared by YAMAGUCHI's procedure[12], with 2 M aq methanolic sodium hydroxide at 60°C gave the mono-acid (**10**). Subsequently, the acid chloride (**11**), obtained upon treatment of **10** with oxalyl chloride, was heated with 2-mercaptopyridine *N*-oxide sodium salt in toluene, decarboxylative rearrangement occurring to give the pyridyl sulfide (**12**). The use of DMAP (BARTON's method) also provided **12** but reduced the yield to less than 10%. The presence of two electron-withdrawing groups made

Scheme 3. Alternative route to **8** *via* radical decarboxylation.



Scheme 4. Preparation of the outer-ring diene (**14**).



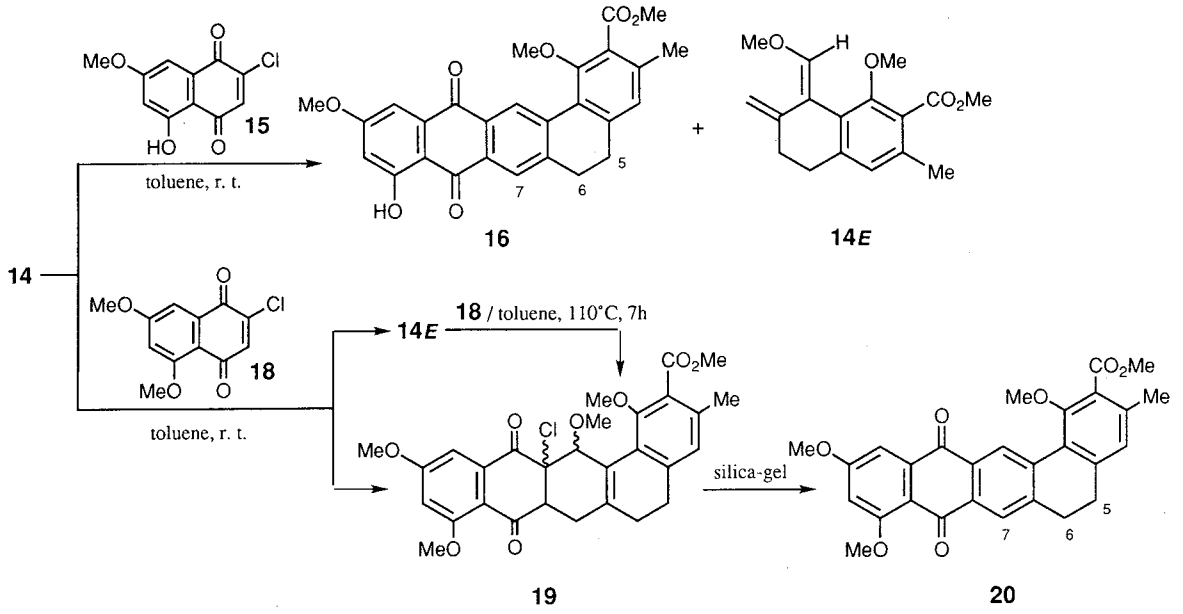
the benzylic methylene group more acidic, which resulted an unexpected nucleophilic reaction at the benzylic position more easily in the presence of base such as DMAP. The reductive desulfurization of **12** with nickel boride afforded the desired tri-substituted α-tetralone (**8**) in 75% over all yield from **9**. The one-pot direct radical decarboxylation of **10** (2-mercaptopyridine *N*-oxide, DCC, DMAP/tributylstannane)[11] failed.

Construction of the Substituted 5,6-Dihydrobenzo[*a*]naphthacenequinone

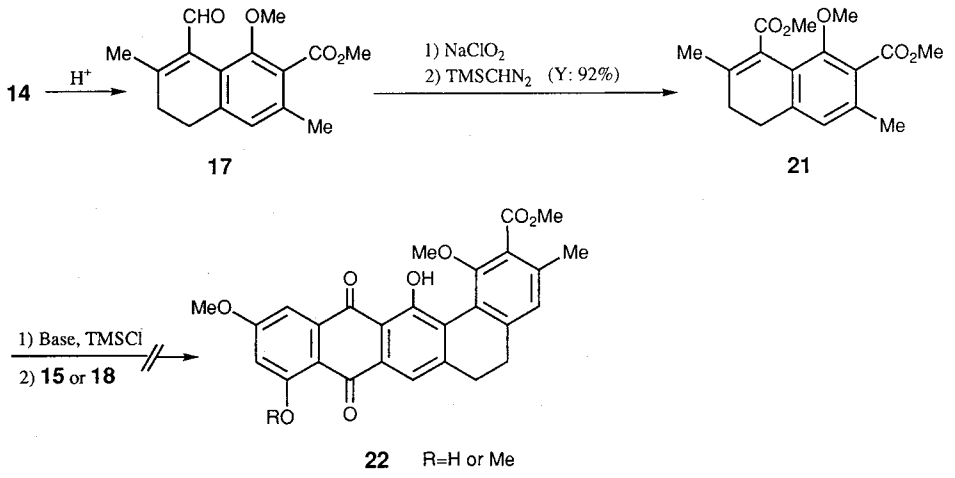
Compound **8** was converted to the outer-ring methoxydiene (**14**) in a four-step operation (Scheme 4). Namely, MANNICH reaction of **8**, followed by WITTIG reaction with (methoxymethylene)phophorane at 0°C afforded a *Z*/*E* mixture (approximately 5:4 ratio, δ 6.05 for *Z*-isomer and δ 7.03 for *E* in ^{1}H NMR) of the enol methyl ethers (**13**) in 35% yield. The reaction temperature influenced the ratio of two isomers. Thus, the reaction at −15°C gave a 1:2 ratio of *Z*:*E*, which shifted to a 2:1 ratio at 25°C. Furthermore, when this reaction was investigated by using other bases such as LDA, sodium hydride, butyllithium and sodium bis(trimethylsilyl)amide, the yield of **13** was not improved and little or no desired **13** was detected. We considered that steric hindrance, instability (keto-amine, **13** and Wittig reagent) and low reactivity (bearing two electron-donating groups in the *ortho* and *para* orientations) resulted in a low yield. The two isomers of **13** could not be separated completely. Treatment of **13** with *m*-chloroperbenzoic acid, followed by heating in toluene gave **14** which was pure enough for the next DIELS-ALDER reaction without further purification.

Cyclization of **14** with 2-chloro-5-hydroxy-7-methoxynaphthoquinone (**15**)[13] in toluene at room temperature for 2 hours afforded the desired product **16** in 36% yield along with the unreacted minor *E*-diene (**14***E*) (Scheme 5). The two compounds were easily separable by trituration with hexane since **14***E* was soluble in hexane. The dienophile (**15**) reacted more rapidly with **14***Z* than with **14***E* and this difference could be used to separate **14***E* from mixture. The stereochemistry of **14***E* was tentatively determined by NOE experiments. Significant enhancements were observed between 1-OMe (δ 3.69) and the enolic H (δ 7.18), and the enolic OMe (δ 3.81) and the vinylic H (δ 5.75). Extending the reaction time, raising the reaction temperature or adding LEWIS acid did not improve the yield. The aldehyde (**17**) was obtained in-

Scheme 5. DIELS-ALDER reactions of **14** with naphthoquinones (**15** and **18**).



Scheme 6. Attempt synthesis of the A-ring tri-substituted 14-hydroxy-5,6-dihydrobenzo[*a*]naphthacenequinone (**22**).

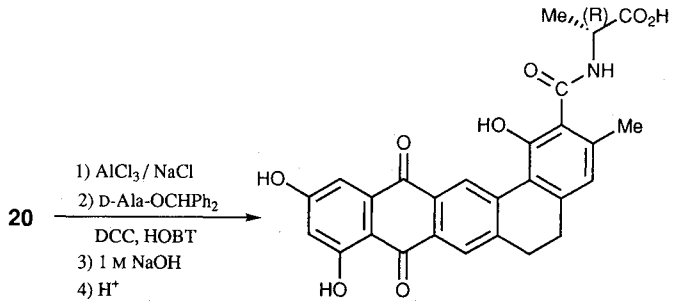


stead of **14***E*. Various conditions for cyclization of the recovered **14***E* to **16** were attempted, but only traces of **16** were detected and again, **17** was a main product.

Interestingly, treating **14** with 2-chloro-5,7-dimethoxynaphthoquinone (**18**)[13] under the same condition as described for **16** gave the intermediate (**19**) and **14***E*. Under more forcing condition, heating with **18** in toluene for 7 hours, **19** can also be obtained from **14***E*. The initial adduct **19** did not undergo elimination of hydrogen chloride and methanol *in situ*, but upon treatment with silica-gel in chloroform **20** was formed in 75% yield from **14**. These results indicated that the hydrogen chloride, liberated from the aromatization of DIELS-ALDER adduct, caused the less reactive **14***E* to decompose to **17**. The structures of **16** and **20** were entirely confirmed by the HMBC correlations between 7-H (δ 8.14 and δ 8.10) and C-8 (δ 186.7 and δ 181.3) respectively. As expected, the DIELS-ALDER reaction proceeded regiospecifically, and no regioisomeric product was detected.

Oxidation of the aldehyde (**17**), obtained from hydrolysis of **14** with 1 M hydrochloric acid, to its corresponding ester (**21**) was achieved either in 92% yield by a two-stage process involving reaction with sodium chlorite, followed by treatment of the resulting product with (trimethylsilyl)diazomethane, or in less than 10% yield by COREY's one-pot procedure[14]. Cyclization of **21** with **15** or **18**

Scheme 7. Introduction of D-alanine into the C-15 position of **20**.



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was attempted under various conditions without success (Scheme 6). The starting material (**21**) was recovered, presumably because the vinylketene acetal did not form. This reaction is currently under investigation.

Finally, in order to introduce the amino acid moiety into the C-15 position and to remove methyl ethers, demethylation of **20** was carried out in an aluminium chloride/sodium chloride melt[15]. The obtained acid was coupled with protected D-alanine using the active ester method and then deprotected by treating with 1 M sodium hydroxide, followed by acidification with 1 M hydrochloric acid to give **23** in 48% overall yield from **20** (Scheme 7).

We have synthesized the key intermediate **8** and applied it to the synthesis of the substituted benzo[*a*]naphthacenequinone successfully. We believe that **8** will also be 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.

Experimental

General

Mass spectra (FAB-MS) were measured on a Jeol SX102 mass spectrometer. ^1H (400 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Jeol JNM-EX400 and JNM-ALPHA500 spectrometers, respectively, in $CDCl_3$ unless otherwise noted. UV spectra was recorded on a Hitachi U-3210 spectrometer. Melting points were determined on a Yanagimoto micro melting points apparatus.

Methyl 8-Methoxy-6-methyl-1-oxo-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (8)

(A) From Methyl 8-Methoxy-7-(methoxycarbonyl)-1-oxo-1,2,3,4-tetrahydro-6-naphthylacetate (**9**)

A solution of methyl 8-methoxy-7-(methoxycarbonyl)-1-oxo-1,2,3,4-tetrahydro-6-naphthylacetate (**9**) (1.835 g, 6 mmol) and sodium methoxide (972 mg, 18 mmol) in MeOH - H_2O (4 : 1, 80 ml) was heated at 60°C for 20 hours. After evaporation, the residue was dissolved in water. The solution was washed with diethyl ether, acidified with 2 M HCl under cooling and extracted with chloroform. The chloroform solution was washed with water and satd NaCl solution, dried over anhydr Na_2SO_4 and evaporated to afford 8-methoxy-7-(methoxycarbonyl)-1-oxo-1,2,3,4-tetrahydro-6-naphthylacetic acid (**10**) as a solid (1.75 g). MP 142°C. ^1H NMR δ 2.09 (2H, m, 3-H_2), 2.65 (2H, m, 2-H_2), 2.96 (2H, m, 4-H_2), 3.68 (2H, s, CH_2CO_2H), 3.85 (3H, s, OCH_3), 3.93 (3H, s, CO_2CH_3), 7.02 (1H, s, 5-H).

A suspension of the acid (**10**) (1.75 g) and oxalyl chloride (3.2 ml) in anhydr toluene (50 ml) was stirred at room temperature under an argon atmosphere for 15 hours. After evaporation, methyl 6-chlorocarbonylmethyl-8-methoxy-1-oxo-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (**11**) was obtained. ^1H NMR δ 2.11 (2H, m, 3-H_2), 2.67 (2H, m, 2-H_2), 2.96 (2H, m, 4-H_2), 3.86 (3H, s, OCH_3), 3.93 (3H, s, CO_2CH_3), 4.19 (2H, s, CH_2COCl), 6.95 (1H, s, 5-H). A solution of the acid chloride (**11**) in anhydr toluene (25 ml) was added to a stirred azeotropically dried (DEAN-STARK apparatus) suspension of 2-mercaptopyridine *N*-oxide sodium salt (1.6 g) in toluene (90 ml) at reflux in one portion. After 30 minutes, the reaction mixture was washed with water and satd NaCl solution, dried over anhydr Na_2SO_4 and concentrated. The residue was chromatographed on

silica-gel with chloroform - MeOH (49 : 1) to give methyl 8-methoxy-1-oxo-6-(2-pyridylthio)methyl-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (**12**) (1.563 g). FAB-MS *m/z* 358 ($[M+H]^+$). ^{1}H NMR δ 2.05 (2H, m, 3-H_2), 2.61 (2H, m, 2-H_2), 2.90 (2H, m, 4-H_2), 3.86 (3H, s, OCH_3), 3.93 (3H, s, CO_2CH_3), 4.19 (2H, s, CH_2SAr), 7.01 (1H, m, Ar-H), 7.15 (1H, d, J=8.3 Hz, Ar-H), 7.19 (1H, s, 5-H), 7.48 (1H, m, Ar-H), 8.44 (1H, m, Ar-H).

A solution of $NaBH_4$ (3.45 g, 90.8 mmol) in EtOH - H_2O (1 : 1, 50 ml) was cautiously added to a mixture of nickel chloride hexahydrate 10.71 g (45.4 mmol) and boric acid (2.82 g, 45.4 mmol) in EtOH (100 ml) at 0°C under an argon atmosphere. To this mixture a solution of compound **12** (1.08 g, 3.03 mmol) in EtOH (20 ml) was added. The reaction mixture was heated for 1.5 hours. The precipitate was filtered off on celite and the filtrate was evaporated. The residue was partitioned between aq satd $NaHCO_3$ solution and chloroform. The chloroform layer was washed with water, satd NaCl solution and dried over anhydr Na_2SO_4 and evaporated to afford **8** (710 mg). MP 106°C (recrystallized from EtOH). FAB-MS *m/z* 249 ($[M+H]^+$). IR ($CHCl_3$) cm^{-1} 1725, 1680, 1600. ^{1}H NMR 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), 6.87 (1H, s, 5-H).

Anal Calcd for $C_{14}H_{16}O_4$: C 67.73, H 6.50.
Found: C 67.42, H 6.55.

(B) From Ethyl 3-Methyl-1-oxo-2-cyclohexene-2-carboxylate (**2**)

Ethyl 3-Methyl-1-oxo-2-cyclohexene-2-carboxylate (**2**):

To a solution of acetobutyric acid (14.3 g, 110 mmol) in anhydr THF (500 ml) was added carbonyldiimidazole (19.44 g, 120 mmol). After stirring at room temperature for 6 hours, the magnesium salt prepared from magnesium ethoxide (6.84 g, 60 mmol) and monoethyl malonate (15.84 g, 120 mmol) was added. The reaction mixture was stirred for 18 hours. After filtration and evaporation, the residue was partitioned between diethyl ether and 0.5 M HCl. The diethyl ether layer was washed with satd $NaHCO_3$ solution, water and satd NaCl solution and dried over anhydr Na_2SO_4. After evaporation, **2** (16 g) was obtained. MP 44~45°C. IR ($CHCl_3$) cm^{-1} 1725, 1670, 1635. ^{1}H NMR δ 1.33 (3H, t, J=7 Hz, CH_2CH_3), 1.97~2.04 (2H, m, 5-H_2), 2.37~2.46 (4H, m, 4- and 6-H_2), 4.31 (2H, q, J=7 Hz, CH_2CH_3).

Anal Calcd for $C_{10}H_{14}O_3$: C 65.92, H 7.74.
Found: C 66.23, H 7.60.

Ethyl 6-Ethylenedioxy-2-methyl-1-cyclohexene-1-carboxylate (**3**):

A mixture of compound **2** (2.73 g, 15 mmol), ethylene glycol (20 ml) and *p*-toluenesulfonic acid monohydrate (160 mg, 0.84 mmol) in benzene (100 ml) was refluxed for 36 hours under a DEAN-STARK trap. After washing with satd $NaHCO_3$ solution and evaporation, the residue was chromatographed on silica-gel with chloroform to give **3** (2.71 g). ^{1}H NMR δ 1.31 (3H, t, J=7 Hz, CH_2CH_3), 1.71~1.84 (4H, m, 4- and 5-H_2), 2.10 (2H, m, 3-H_2), 3.93~4.06 (4H, m, acetal), 4.23 (2H, q, J=7 Hz, CH_2CH_3).

Methyl 8,8-Ethylenedioxy-3-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydro-2-naphthalenecarboxylate (**4**):

A solution of compound **3** (2.26 g, 10 mmol) in anhydr THF (12 ml) was added to a 2.0 M LDA solution (17.5 ml, 35 mmol) at −78°C. The stirring was continued at −78°C for 1 hour and 0°C for 1.5 hours. Methyl crotonate (4.5 g, 45 mmol) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 15 hours. After quenching with satd NH_4Cl solution and extracting with chloroform, the organic layer was evaporated. The residue was chromatographed on silica-gel with chloroform to give **4** (840 mg), ethyl 2-(2-hydroxyethoxy)-6-methylbenzoate (**5**) (560 mg) and methyl 8-(2-hydroxyethoxy)-3-methyl-1-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (**6**) (417 mg). Compound **4**: MP 121~122°C (recrystallized from MeOH). FAB-MS *m/z* 281 ($[M+H]^+$). ^{1}H NMR δ 1.02 (3H, d, J=6.6 Hz, 3-CH_3), 3.09 (1H, d, J=12.5 Hz, 2-H), 3.77 (3H, s, CO_2CH_3), 3.90~4.00 (2H, m, acetal-H_2), 4.21~4.34 (2H, m, acetal-H_2).

Anal Calcd for $C_{15}H_{20}O_5$: C 64.27, H 7.19.
Found: C 64.40, H 7.07.

Compound **5**:

FAB-MS *m/z* 225 ($[M+H]^+$). ^{1}H NMR δ 1.39 (3H, t, J=7.3 Hz, CH_2CH_3), 2.32 (3H, s, 6-CH_3), 3.86 (2H, t, J=4.4 Hz, acetal-H_2), 4.17 (2H, t, J=4.4 Hz, acetal-H_2), 4.41 (2H, q, J=7.3 Hz, CH_2CH_3), 6.80 (1H, d, J=8.3 Hz, Ar-H), 6.84 (1H, d, J=7.8 Hz, Ar-H), 7.24 (1H, dd, J=8.3 and 7.8 Hz, 4-H). Compound **6**: FAB-MS *m/z* 279 ($[M+H]^+$). ^{1}H NMR δ 1.13 (3H, d, J=6.4 Hz, 3-CH_3), 2.63 (1H, m, 3-H), 2.70 (1H, dd, J=12.2 and 11.2 Hz, one of 4-H_2), 3.02 (1H, dd, J=12.2 and 3.4 Hz, one of 4-H_2), 3.29 (1H, d, J=11.2 Hz, 2-H), 3.80 (3H, s, CO_2CH_3), 3.92 (2H, t, J=3.9 Hz, acetal-H_2), 4.16 (2H, t, J=3.9 Hz, acetal-H_2), 6.85 (2H, J=7.8 Hz, 5- and 7-H), 7.42 (1H, t, J=7.8 Hz, 6-H).

Methyl 8-Hydroxy-6-methyl-1-oxo-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (**7**):

To a mixture of **4** (560 mg, 2 mmol), molecular sieves 4A (powder, 5 g) in anhydr MeOH (15 ml) was added cerium (IV) ammonium nitrate (548 mg, 1 mmol) and a

solution of iodine (254 mg) in anhydr MeOH (11 ml) at 0°C. The reaction mixture was heated at 70°C for 7 hours. After filtration, the filtrate was concentrated. The residue was dissolved in EtOAc, washed with water and satd NaCl solution, dried over anhydr Na_2SO_4 and evaporated. The residue was chromatographed on silica-gel with chloroform - hexane (1 : 1) to afford **7** (94 mg). MP 69~70.5°C (recrystallized from EtOH). EI-MS *m/z* 234 (M^+). ^1H NMR δ 2.09 (2H, m, 3-H_2), 2.32 (3H, s, 6-CH_3), 2.68 (2H, m, 2-H_2), 2.89 (2H, m, 4-H_2), 3.93 (3H, s, CO_2CH_3), 6.58 (1H, s, 5-H), 12.90 (1H, s, OH).

Anal Calcd for $C_{13}H_{14}O_4$: C 66.66, H 6.02.
Found: C 66.74, H 6.04.

Compound (**8**):

A mixture of **7** (468 mg, 2 mmol), methyl iodide (1.42 g, 10 mmol) and K_2CO_3 (1.656 g, 12 mmol) in acetone (50 ml) was refluxed for 20 hours under an argon atmosphere. After filtration, the filtrate was concentrated and chromatographed on silica-gel with EtOAc - hexane (3 : 2) to give **8** (410 mg).

Methyl 2-(Dimethylamino)methyl-8-methoxy-1-methoxymethylene-6-methyl-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (**13**)

A mixture of compound **8** (890 mg, 3.59 mmol), dimethylammonium chloride (440 mg, 5.44 mmol), paraformaldehyde (180 mg, 2 mmol) and 3 drops of conc HCl in 95% EtOH (3 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. The chloroform solution was dried over anhydr Na_2SO_4 and evaporated to afford methyl 2-(dimethylamino)methyl-8-methoxy-6-methyl-1-oxo-1,2,3,4-tetrahydro-7-naphthalenecarboxylate (937 mg). ^1H NMR δ 1.83~1.93 (1H, m, one of 3-H_2), 2.25 (6H, s, $N(CH_3)_2$), 2.29 (3H, s, 6-CH_3), 2.26~2.34 (1H, m, one of 3-H_2), 2.50 (1H, dd, J=11.7 and 9.2 Hz, one of $CH_2N(CH_3)_2$), 2.64 (1H, m, 2-H), 2.72 (1H, dd, J=11.7 and 4.9 Hz, one of $CH_2N(CH_3)_2$), 2.87~3.01 (2H, m, 4-H_2) 3.83 (3H, s, OCH_3), 3.91 (3H, s, CO_2CH_3), 6.86 (1H, s, 5-H).

To a suspension of (chloromethyl)triphenylphosphonium chloride (3.426 g, 10 mmol) in anhydr THF (20 ml) was added 1.8 M phenyllithium in cyclohexane-diethyl ether solution (5 ml, 9 mmol) at −45°C. After stirring at the same temperature for 30 minutes, a solution of above keto-amine (305 mg, 1 mmol) in anhydr THF (5 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, dried over anhydr Na_2SO_4 and evaporated. The residue was dissolved in diethyl ether, washed with water 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 **13** (120 mg). ^1H NMR δ 3.63 and 3.74 (each 5/3H, s, OCH_3), 3.68 and 3.69 (each 4/3H, s, OCH_3), 3.90 and 3.92 (5/3H and 4/3H, s, CO_2CH_3), 6.05 and 7.01 (5/9H and 4/9H, s, enolic olefin H), 6.71 and 6.72 (5/9H and 4/9H, s, 5-H).

Methyl 1-Methoxy-8-methoxymethylene-3-methyl-7-methylene-5,6,7,8-tetrahydro-2-naphthalenecarboxylate (**14**)

A solution of *m*CPBA (114 mg, 0.66 mmol) in chloroform (4 ml) was added to a solution of compound **13** (220 mg, 0.66 mmol) in chloroform (5 ml) at 0°C. After stirring at the same temperature for 15 minutes, the reaction mixture was passed through a column of basic alumina (pH 10) with chloroform~chloroform - MeOH (19 : 1) to give methyl 2-(dimethylamino)methyl-8-methoxy-1-methoxymethylene-6-methyl-1,2,3,4-tetrahydro-7-naphthalenecarboxylate *N*-oxide (200 mg). ^1H NMR δ 2.22 and 2.25 (4/3H and 5/3H, s, CH_3), 3.16 and 3.22 (each 5/3H, s, $N(CH_3)_2$), 3.24 and 3.28 (each 4/3H, s, $N(CH_3)_2$), 3.92 and 3.93 (5/3H and 4/3H, s, CO_2CH_3), 6.36 and 7.11 (5/9H and 4/9H, s, enolic olefin H), 6.71 and 6.74 (5/9H and 4/9H, s, 5-H).

A solution of the above *N*-oxide (30 mg, 0.086 mmol) in anhydr toluene (3 ml) was heated at 90°C for 30 minutes under argon atmosphere. After evaporation, compound **14** (25 mg) was obtained. FAB-MS *m/z* 288 (M^+). ^1H NMR δ 2.23 and 2.26 (4/3H and 5/3H, s, CH_3), 3.67 and 3.72 (each 5/3H, s, OCH_3), 3.69 and 3.81 (each 4/3H, s, OCH_3), 3.90 and 3.92 (5/3H and 4/3H, s, CO_2CH_3), 4.61 and 5.10 (each 5/9H, d, J=1.5 Hz, olefin H), 5.23 and 5.75 (each 4/9H, d, J=1.5 Hz, olefin H), 6.53 and 7.18 (5/9H and 4/9H, s, enolic olefin H), 6.74 and 6.75 (4/9H and 5/9H, s, 4-H).

1,11-Dimethoxy-9-hydroxy-2-methoxycarbonyl-3-methyl-5,6-dihydrobenzo[*a*]naphthacene-8,13-dione (**16**)

To a solution of compound **14** (25 mg, 0.086 mmol) in anhydr toluene (2 ml) was added 2-chloro-5-hydroxy-7-methoxy-1,4-naphthoquinone (**15**) (21 mg, 0.086 mmol) at room temperature. After stirring for 2 hours, the reac-

tion mixture was adjusted to pH 9 with satd $NaHCO_3$ solution and extracted with chloroform. The organic layer was washed with water and satd NaCl solution, dried over anhydr Na_2SO_4 and evaporated. The residue was extracted with hexane. Evaporation gave **14*E*** (10 mg). FAB-MS *m/z* 288 (M^+). ^1H NMR 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, 2 × 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), 7.18 (1H, s, enolic olefin H). ^{13}C NMR (125 MHz) δ 18.8 (3-CH_3), 30.7 (C-5), 33.6 (C-6), 52.2 (CO_2CH_3), 60.5 (1-OCH_3), 61.1 (enolic OCH_3), 108.9 (C-8), 112.3 (7-C), 124.9 (C-4), 125.9 (C-8a), 127.5 (C-2), 132.5 (C-3), 140.5 (C-7), 142.8 (C-4a), 151.3 (8-C), 153.0 (C-1), 169.2 (2-CO_2).

The insoluble material was chromatographed on silica-gel with chloroform to give **16** (18 mg). MP 295~296°C (dec). FAB-MS *m/z* 459 ($[M+H]^+$). ^1H NMR 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), 3.95 (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), 12.95 (1H, s, 9-OH). ^{13}C NMR δ 19.3 (C-16), 29.1 (C-5), 29.6 (C-6), 52.4 (CO_2CH_3), 56.0 (11-OCH_3), 61.7 (1-OCH_3), 106.5 (C-10), 107.6 (C-12), 111.0 (C-8a), 123.3 (C-14b), 125.7 (C-4), 125.9 (C-7), 126.4 (C-14), 128.8 (C-2), 131.8 (C-7a), 132.7 (C-13a), 135.4 (C-12a), 137.4 (C-3), 137.9 (C-14a), 142.1 (C-4a), 144.6 (C-6a), 155.8 (C-1), 165.3 (C-9), 166.3 (C-11), 168.5 (C-15), 182.3 (C-13), 186.7 (C-8). UV λ_{max}^{MeOH} nm (ε) 229 (sh, 23,300), 252 (sh, 11,100), 289 (sh, 27,900), 299 (35,400), 322 (sh, 10,800), 362 (sh, 4,000), 423 (6,900).

2-Methoxycarbonyl-3-methyl-1,9,11-trimethoxy-5,6-dihydrobenzo[*a*]naphthacene-8,13-dione (**20**)

(a) To a solution of compound **14** (144 mg, 0.5 mmol) in anhydr toluene (3 ml) was added 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (**18**) (152 mg, 0.6 mmol) at room temperature for 2 hours. After evaporation, the residue was treated with hexane to give **14*E*** (60 mg) and an insoluble compound **19**. FAB-MS *m/z* 541 $(MH)^+$. ^1H NMR δ 2.78 (3H, s, 14-OCH_3), 5.36 (1H, s, 14-H). Compound **19** was stirred with silica-gel in chloroform for 18 hours. After filtration and evaporation, the residue was chromatographed on silica-gel with chloroform to afford **20** (102 mg). MP 240~241°C (dec). FAB-MS *m/z* 473 (MH^+). IR ($CHCl_3$) cm^{-1} 1725, 1670, 1658, 1600. ^1H NMR 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, br 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), 9.15 (1H, s, 14-H). ^{13}C NMR δ 19.2 (C-16), 29.2 (C-5), 29.7 (C-6), 52.3 (CO_2CH_3), 56.0 (11-OCH_3), 56.6 (9-OCH_3), 61.6 (1-OCH_3), 103.3 (C-12), 104.7 (C-10), 116.3 (C-8a), 123.4 (C-14b), 125.6 (C-14), 125.7 (C-4), 126.3 (C-7), 128.7 (C-2), 131.6 (C-13a), 133.6 (C-7a), 136.6 (C-14a), 136.9 (C-3), 137.9 (C-12a), 142.2 (C-4a), 144.8 (C-6a), 155.7 (C-1), 162.5 (C-9), 164.7 (C-11), 168.7 (C-15), 181.3 (C-8), 183.3 (C-13). UV λ_{max}^{MeOH} nm (ε) 218 (sh, 40,400), 230 (41,700), 295 (57,400), 316 (sh, 20,200), 360 (sh, 6,900), 405 (8,800).

Anal Calcd for $C_{28}H_{24}O_7$: C 71.18, H 5.12.
Found: C 71.01; H 4.92.

(b) A solution of compound **14*E*** (52 mg, 0.18 mmol) and 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (**18**) (51 mg, 0.2 mmol) in anhydr toluene (1.5 ml) was heated at 110°C for 7 hours. After removal of the solvent, the residue (compound **19**) was treated with silica-gel in chloroform as in (a) to afford **20** (70 mg).

Methyl 3,7-Dimethyl-8-formyl-1-methoxy-5,6-dihydro-2-naphthalenecarboxylate (**17**)

To a solution of **14** (240 mg, 0.83 mmol) in dioxane (2 ml) was added 1 M HCl (0.4 ml) at room temperature. After 30 minutes, the reaction mixture was extracted with chloroform. The chloroform layer was washed with water, satd NaCl solution, dried over anhydr Na_2SO_4 and evaporated to give **17** (228 mg). ^1H NMR δ 2.25 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.31 (2H, m, 6-H_2), 2.69 (2H, m, 5-H_2), 3.55 (3H, s, 1-OCH_3), 3.93 (3H, s, CO_2CH_3), 6.85 (1H, s, 4-H), 9.81 (1H, s, CHO).

Methyl 3,7-Dimethyl-1-methoxy-8-methoxycarbonyl-5,6-dihydro-2-naphthalenecarboxylate (**21**)

(a) To a solution of **17** (91 mg, 0.3 mmol) and 2-methyl-2-butene (1.8 ml) in *t*-BuOH (7.5 ml) was added a solution of sodium chlorite (300 mg, 3.32 mmol) and sodium phosphate monobasic (390 mg, 2.52 mmol) in water (3 ml) at room temperature. After stirring at the same temperature for 1.5 hours, the solvent was evaporated. The residue was dissolved in EtOAc. The EtOAc solution was washed with water and satd NaCl solution, dried over anhydr Na_2SO_4, and evaporated to give an acid (81 mg). ^1H NMR δ 2.12 (3H, s, 7-CH_3), 2.25~2.29 (2H, m, 6-H_2), 2.27 (3H, s, 3-CH_3), 2.71 (2H, m, 5-H_2), 3.68 (3H, s, OCH_3), 3.91 (3H, s, CO_2CH_3), 6.80 (1H, s, 4-H). To a solution of this acid (81 mg) in MeOH (2 ml) was added 10% trimethylsilyldiazomethane in hexane solution (0.3 ml). After stirring for 5 hours, the solvent

was evaporated to afford **21** (85 mg). MP 116~118°C. FAB-MS *m/z* 305 ($[M+H]^+$). ^1H NMR δ 2.04 (3H, s, 7-CH_3), 2.23~2.27 (2H, m, 6-H_2), 2.26 (3H, s, 3-CH_3), 2.70 (2H, m, 5-H_2), 3.61 (3H, s, OCH_3), 3.77 (3H, s, CO_2CH_3), 3.90 (3H, s, CO_2CH_3), 6.78 (1H, s, 4-H).

(b) To a mixture of activated manganese dioxide (30.5 mg, 0.35 mmol), sodium cyanide (4.3 mg, 0.086 mmol) and glacial acetic acid (1.8 mg, 0.029 mmol) in MeOH (0.3 ml) was added a solution of **17** (8 mg, 0.029 mmol) in MeOH (0.2 ml). After stirring at room temperature for 15 hours, the insoluble material was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform, washed with water 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 **21** (0.8 mg).

(8,13-Dioxo-3-methyl-1,9,11-trihydroxy-5,6-dihydrobenzo[*a*]naphthacen-2-yl)carbonyl-D-alanine (**23**)

Compound **20** (47 mg, 0.1 mmol) was added to a melt of anhydrous aluminium chloride (2.5 g) and sodium chloride 500 mg at 150°C under argon atmosphere. After stirring for 5 minutes, 1 M HCl (10 ml) was added under cooling. The resulting mixture was warmed to 50°C for 5 minutes. After cooling the precipitates were collected by centrifugation. The obtained solid was chromatographed on silica-gel with chloroform - EtOH - pyridine (1 : 1 : 1) to give a dark red powder, which was dissolved in 1 M NaOH then acidified with 1 M HCl to pH 2. The precipitates were collected by centrifugation to give 2-hydroxycarbonyl-3-methyl-1,9,11-trihydroxy-5,6-dihydrobenzo[*a*]naphthacene-8,13-dione (36 mg). MP 268~271°C (dec). FAB-MS (negative) *m/z* 415 (M^-). ^1H NMR ($CDCl_3$ - pyridine-d_5 (1 : 1)) δ 2.72 and 2.82 (each 2H, m, 5- and 6-H_2), 2.77 (3H, s, 3-CH_3), 6.64 (1H, s, 10-H), 6.80 (1H, s, 4-H), 8.12 (1H, s, 7-H), 9.66 (1H, s, 14-H), 13.30 (1H, bs, OH). UV λ_{max}^{MeOH} nm (ε) 228 (20,400), 268 (sh, 10,700), 299 (19,200), 319 (sh, 11,800), 397 (sh, 2,300), 444 (4,200).

To a suspension of this acid (42 mg, 0.1 mmol) and *N*-hydroxybenzotriazole (40 mg, 0.3 mmol) in acetonitrile (2 ml) was added a solution of D-alanine diphenylmethyl ester *p*-toluenesulfonate (90 mg, 0.2 mmol) and *N*-methylmorpholine (30 mg, 0.3 mmol) in acetonitrile (1 ml) and DCC (40 mg, 0.02 mmol) at 0°C. After stirring at room temperature for 48 hours, the precipitate was filtered and washed with chloroform. The combined organic layer was washed with 10% citric acid solution, satd $NaHCO_3$ solution and water, dried over anhydr Na_2SO_4 and evaporated. The obtained residue was chromatographed on silica-gel with chloroform to give (8,13-dioxo-3-methyl-1,9,11-trihydroxy-5,6-dihydrobenzo[*a*]naphthacen-2-yl)carbonyl-D-alanine diphenylmethyl ester (37 mg). MP 231°C (dec). FAB-MS *m/z* 654 ($[M+H]^+$). ^1H NMR ($CDCl_3$ - CD_3OD (10 : 1)) δ 1.61 (3H, d, J=7.3 Hz, $CHCH_3$), 2.54 (3H, s, 3-CH_3), 2.81 and 2.94 (each 2H, m, 5- and 6-H_2), 4.97 (1H, q, J=7.3 Hz, $CHCH_3$), 6.64 (1H, d, J=2.4 Hz, 10-H), 6.67 (1H, s, $CHPh_2$), 6.95 (1H, s, 4-H), 7.26 (1H, d, J=2.4 Hz, 12-H), 8.09 (1H, s, 7-H), 9.27 (1H, s, 14-H).

The above diphenylmethyl ester (20 mg) was treated with 1 M NaOH (0.3 ml) in MeOH (0.3 ml) at room temperature for 2 hours. The reaction mixture was adjusted to pH 2 with 1 M HCl under cooling. A similar procedure described for above acid afforded **23** (14 mg). MP 268~270°C (dec). FAB-MS *m/z* 488 ($[M+H]^+$). HRFAB-MS Found: *m/z* 488.1369 (M^+), Calcd. for $C_{27}H_{22}NO_8$: 488.1345. ^1H NMR ($CDCl_3$ - Pyridine-d_5 (1 : 1)) δ 1.68 (3H, d, J=7.3 Hz, $CHCH_3$), 2.57 (3H, s, 3-CH_3), 2.67 and 2.77 (each 2H, m, 5- and 6-H_2), 5.01 (1H, m, $CHCH_3$), 6.58 (1H, s, 10-H), 6.79 (1H, s, 4-H), 7.52 (1H, s, 12-H), 8.11 (1H, s, 7-H), 9.52 (1H, s, 14-H), 13.30 (1H, bs, OH). UV λ_{max}^{MeOH} nm (ε) 227 (25,800), 256 (sh, 14,600), 267 (sh, 14,500), 299 (27,300), 324 (sh, 13,500), 368 (sh, 5,000), 434 (6,900).

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