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SYNTHETIC STUDIES ON NOGALAMYCIN CONGENERS [3][1,2] TOTAL SYNTHESES OF (+)-NOGARENE, (+)-7-DEOXYNOGAROL, AND (+)-7-CON-*O*-METHYLNOGAROL

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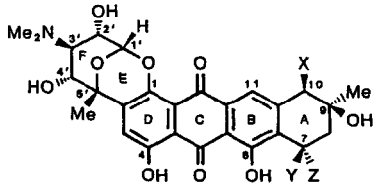
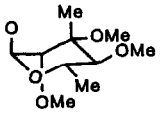
Abstract: According to the retrosynthetic perspective, the title total syntheses were accomplished by employing the regioselective Diels-Alder reactions of the (+)-naphthoquinone (**5**), the CDEF-ring system of nogalamycin congeners, with various structural types of dienes (**8**, **16**, and **26**). The highly functionalized dienes (**16** and **26**) incorporating all the functionalities present in the A-rings of (+)-7-deoxynogarol (**3**) and (+)-7-con-*O*-methylnogarol (**2**), were prepared efficiently by way of the 1,4-cyclohexadiene and 2-cyclohexanone derivatives (**6** and **21**), respectively. Reaction mechanism of the key Diels-Alder reaction was also discussed in terms of its stereoselectivity.

Nogalamycin (**1**) and its congeners are well-known as notable members of the anthracycline family due to their characteristic structures and prominent antitumor activity.[2] Especially, 7-con-*O*-methylnogarol (**2**), the semisynthetic derivative of **1**, has been subjected to clinical trials because of its broad spectrum activity and lower cardiotoxicity than that observed for adriamycin.[2]

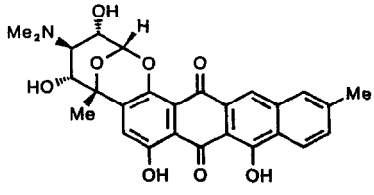
From the retrosynthetic perspective on nogalamycin congeners, the construction of their 11-deoxyanthracyclinone skeletons by the regioselective Diels-Alder reac-



X = CO_2Me, Y = H, Z =  **1**

X = H, Y = OMe, Z = H **2**

X = Y = Z = H **3**



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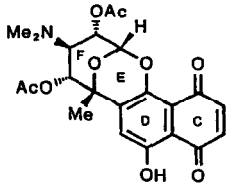


5

tions employing the naphthoquinone (5), the CDEF-ring system of 1 nogalamycin congeners, as a dienophile, was anticipated to hold promise as one of the most convenient and flexible synthetic routes. Based on this synthetic strategy, we have already completed the stereocontrolled synthesis of optically pure (+)-5.[1a,b,2] With 5 in hand, we next examined the regioselective Diels-Alder reaction of 5, the key step of our synthetic plan, and succeeded in the first total syntheses of (+)-nogarene (4), (+)-7-deoxynogarol (3), and (+)-7-con-*O*-methylnogarol (2). The third part of this series of papers concerns full details of these total syntheses.[1b,c]

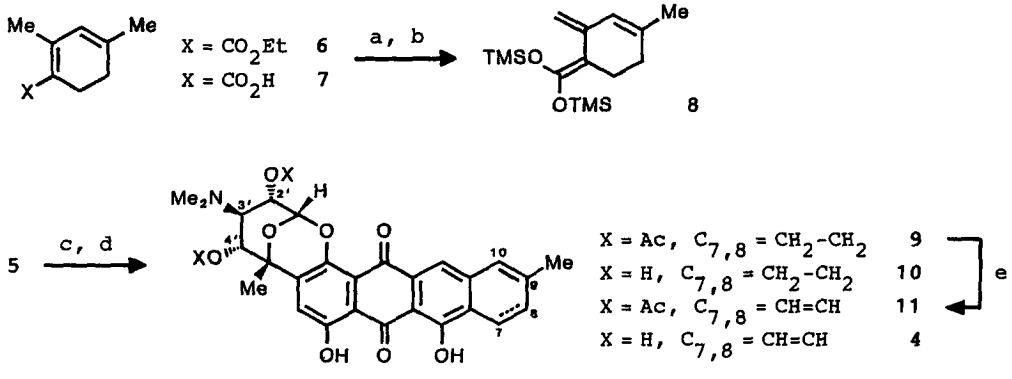
Results and Discussion

Total Synthesis of (+)-Nogarene (4). At first, the total synthesis of (+)-nogarene (4), the simplest congener of 1, was attempted. After preliminary experiments, the bis(trimethylsilyloxy)diene (8) was selected as a favorable diene.[3] For the synthesis of 8, the carboxylic acid (7), mp 92-94 °C, was prepared, as shown in **Scheme 1**, by dealkylation of the ethyl ester (6)[4] with aluminum(III) bromide in tetrahydrothiophene.[5,6] The diene (8) was produced by treating the dianion of 7 with trimethylsilyl chloride.

As expected,[7] the Diels-Alder reaction of the (+)-naphthoquinone (5) with 8, followed by concomitant air oxidation of the addition product during mild acidic work-up, was found to give (+)-2',4'-di-*O*-acetyl-7,8-dihydronogarene (9), mp 171-172 °C and $[\alpha]_D^{20}$ +468° (c 0.112, $CHCl_3$), as a sole product. The regioselectivity observed for this reaction can be well explained by the hypothesis which has been proposed by Boeckman.[8] Acidic hydrolysis of 9 effected clean deacetylation, giving rise to (+)-7,8-dihydronogarene (10), mp 251-257 °C and $[\alpha]_D^{20}$ +571° (c 0.070, $CHCl_3$), the hitherto unknown novel nogalamycin congener.

On the other hand, dehydrogenation of 9 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of dl-10-camphorsulfonic acid (CSA)[9] afforded (+)-2',4'-di-*O*-acetylnogarene (11), mp 177-179 °C and $[\alpha]_D^{20}$ +445° (c 0.062, $CHCl_3$). This was shown to be identical with the authentic sample independently prepared from natural 4 by our hands in all respects (mp, mmp, optical rotation, 400 MHz ^1H NMR, IR, MS). Similar deacetylation of 11 gave (+)-nogarene (4), mp 277-281 °C and $[\alpha]_D^{20}$ +946° (c 0.070, $CHCl_3$). The synthetic sample was found to be

Scheme 1



a) $AlCl_3$, C_4H_8S, rt, 4.5 h, 67% b) LDA, TMSCl, THF, -78 °C → rt, 30 min c) 1) 8, rt, 30 min 2) 3M HCl, rt, 10 min, 85% (from 5) d) 1M HCl, reflux 15 h, 88% (10), 87% (4) e) DDQ, CSA, PhH, reflux, 5 h, 85%.

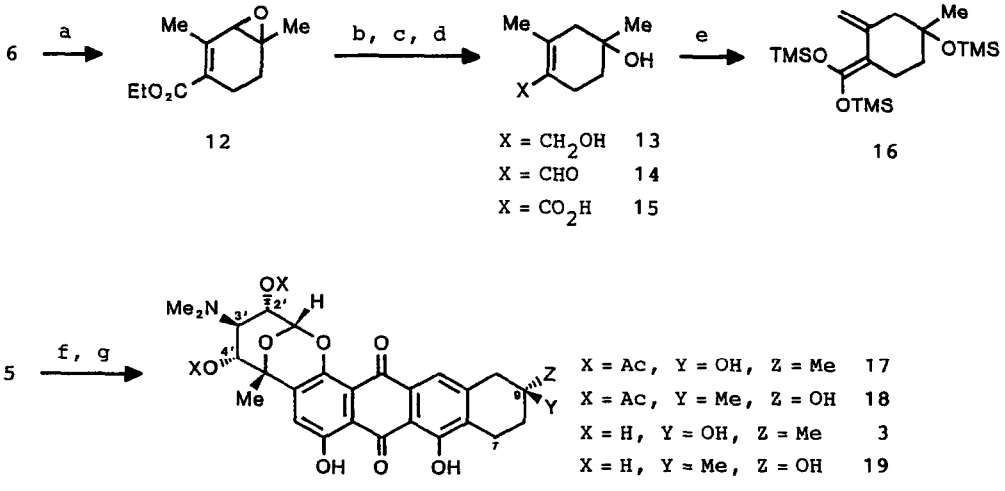
identical with authentic **4** in all respects (mp, mmp, optical rotations, 400 MHz ^{1}H NMR, IR, MS).

Total Synthesis of (+)-7-Deoxynogarol (3). Next, total syntheses of the more highly functionalized nogalamycin congeners such as (+)-7-deoxynogarol (**3**) and (+)-7-con-*O*-methylnogarol (**2**), were attempted based on the results accumulated by the preparation of **4**. Initially, it was expected that the A-rings of **3** and **2** could be readily elaborated by functionalzation of the A-ring of **9**. However, contrary to our expectation, oxidations of the C_9-C_{10} double bond (nogalamycin numbering) of **9** under various conditions were found to produce complex mixtures of reaction products mainly due to preferential oxidative removal of the $C_{3'}$-dimethylamino group.[10] Accordingly, it became desirable to synthesize the complex dienes (**16** and **26**) incorporting all the functionalities involved in the A-rings of **3** and **2**, and to examine the regioselective Diels-Alder reactions of **5** with them.

The synthesis of **3**, the simpler congener than **2**, was first attempted since regioselective Diels-Alder reaction of a highly functionalized dienes such as **16** and **26** had scarcely been studied in the field of anthracyclinone synthesis.[11] As shown in **Scheme 2**, the requisite diene (**16**) could be prepared in a racemic form in short steps. Thus, the γ,δ-double bond of **6**[4] was selectively oxidized to give the epoxy ester (**12**). Reductive opening of the epoxide ring of **12** with lithium triethylborohydride (Superhydride®) was found to proceed regioselectively along with reduction of the ester group, affording the diol (**13**). Stepwise oxidations of **13** to the carboxylic acid (**15**), mp 108–109 °C, by way of the aldehyde (**14**), followed by trapping the trianion of **15** with trimethylsilyl chloride, produced racemic **16**.

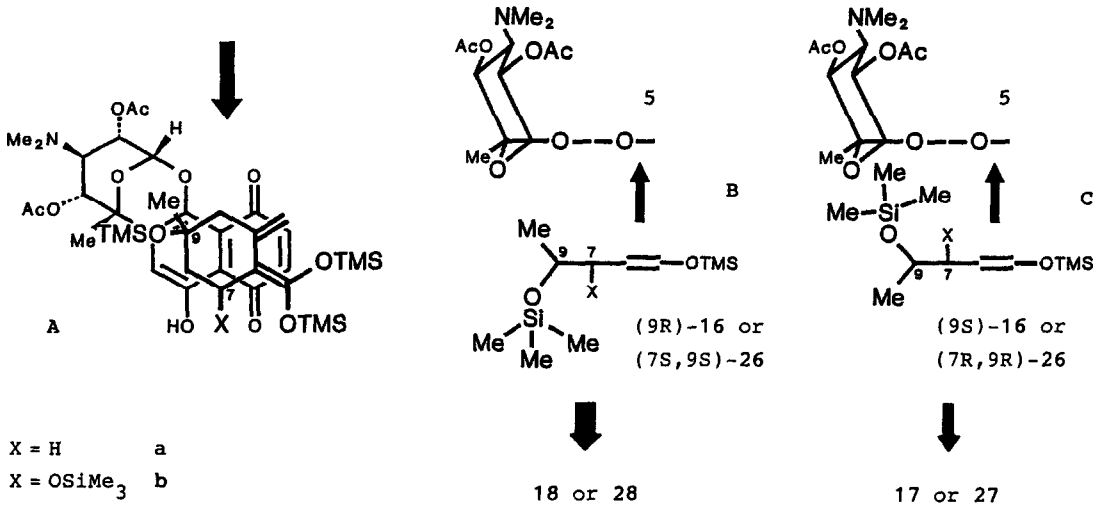
As expected from the model study,[12] the regioselective Diels-Alder reaction of **5** with **16** followed by conomitant air oxidation of the addition products during mild acidic work-up, gave rise to the mixture of (+)-2',4'-di-*O*-acetyl-7-deoxynogarol (**17**) and (+)-2',4'-di-*O*-acetyl-9-*epi*-7-deoxynogarol (**18**) (**17**:**18** = 1:4).

Scheme 2



a) *m*CPBA, PhMe, 0 °C, 2 h, 50% b) $LiEt_3BH$, THF, rt, 2 h, 87% c) MnO_2, THF-C_6H_{14}, rt, 2 h, 88% d) $NaClO_2$, NaH_2PO_4, H_2O-^{t}BuOH-Me_2C=CHMe, 0 °C, 1.5 h, 75% e) LDA, TMSCl, THF, -78 °C → rt, 30 min, f) 1) **16**, THF, 60 °C, 2.5 h 2) 3M HCl, rt, 10 min, 14% (**17**, from **5**), 50% (**18**, from **5**) g) K_2CO_3, MeOH, 50 °C, 20 min, 75% (**3**), 64% (**19**).

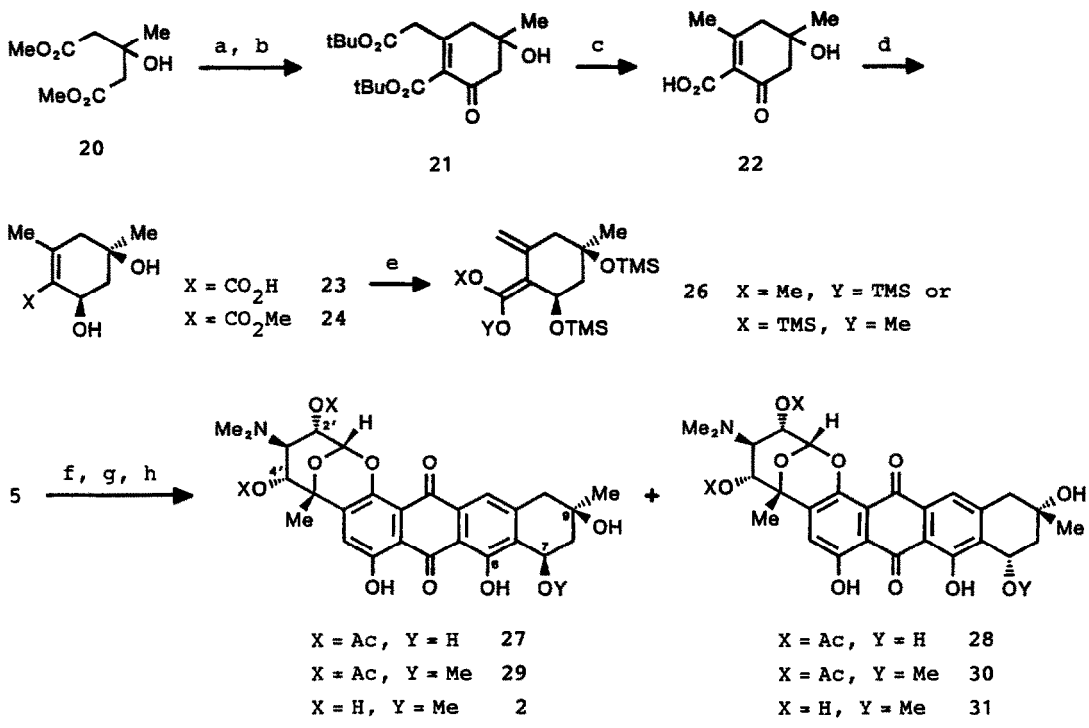
These products (**17** and **18**) could be cleanly separated by TLC, **17**: mp 268-271 °C; $[\alpha]_D^{20}$ +390° (c 0.155, $CHCl_3$), and **18**: mp 182-184 °C; $[\alpha]_D^{20}$ +328° (c 0.102, $CHCl_3$). Synthetic **17** was found to be identical with the authentic sample independently prepared from natural **3** by our hands in all respects (mp, mmp, optical rotation, 400 MHz ^{1}H NMR, IR, MS). Deacetylation of **17** and **18** readily produced natural (+)-7-deoxynogarol (**3**), mp 215-218 °C and $[\alpha]_D^{20}$ +1070° (0.100, $CHCl_3$), and unnatural (+)-9-*epi*-7-deoxynogarol (**19**), mp 215-217 °C and $[\alpha]_D^{20}$ +413° (c 0.135, $CHCl_3$), respectively. Synthetic **3** was identical with authentic **3** in all respect (mp, mmp, optical rotation, 400 MHz ^{1}H NMR, IR, MS).



The notable diastereoselectivity (**17**:**18** = 1:4) observed for the Diels-Alder reaction can be rationalized as follows. Thus, the plausible transition states of the Diels-Alder reaction of **5** with (9R)-**16** and (9S)-**16** are depicted as **Ba** and **Ca**, respectively, by assuming that (1) the Diels-Alder reaction follows the endo-rule and (2) (9R)-**16** and (9S)-**16** approach **5** from the direction opposite to the sterically congested F-ring [the transition state (**Aa**)]. Since steric bulkiness of the C_9-trimethylsilyloxy group is larger than that of the C_9-methyl group, **Ba** seem to be more favored than **Ca** resulting in diastereoselective production of the unnatural **18** by the preferential reaction of **5** with (9R)-**16**.

Total Synthesis of (+)-7-con-*O*-Methylnogarol (2). Being encouraged by completion of the first total synthesis of **3**, the preparation of (+)-7-con-*O*-methylnogarol (**2**) having the more complex structure, was finally examined. However, it turned out to be quite difficult to prepare the precursor of **26** such as the dihydroxy carboxylic acid (**23**) or dihydroxy methyl ester (**24**) due to their increased tendency toward aromatization. After numerous experimentations to overcome these difficulties, synthesis of **24** in short steps could be finally realized as shown in **Scheme 3**, employing the keto diester (**21**) as the starting material. The diester (**21**) was prepared from dimethyl 3-hydroxy-3-methylglutarate (**20**)[13] modifying the procedure reported by Yamaguchi *et al.*[14] Cleavage of the *tert*-butyl esters of **21** with formic acid effected concurrent decarboxylation, giving the keto carboxylic acid (**22**), mp 126-130 °C. The desired *cis*-methyl ester (**24**) was produced along with a small amount of the corresponding *trans*-ester (**25**)[15] by sequential highly stereoselective reduction of **22** and esterification of the resulting carboxylic acids (**23** and its *trans*-isomer). Treatment of the trianion of **24** with trimethylsilyl chloride furnished racemic **26**.

Scheme 3



a) $LiCH_2CO_2{}^tBu$, THF, -78 °C → rt, 4 h b) $Ca(OAc)_2 \cdot H_2O$, MeOH, rt, 10 h, 50% (2 steps) c) HCO_2H, rt, 2 h, 52% d) 1) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, H_2O, rt, 5 min 2) CH_2N_2, ether, rt, 31% (**24**), 3% (**25**) e) LDA, TMSCl, THF, -78 °C → rt, 30 min f) 1) **26**, PhMe, 100 °C, 10 min 2) 3M HCl, rt, 10 min, 45% (from **5**) g) 1) CF_3CO_2H, 0 °C, 3 h 2) NaOMe, MeOH, 0 °C, 5 min, 12% (**29**), 35% (**30**) h) NaOMe, MeOH, 50 °C, 10 min, 92% (**2**), 77% (**31**).

The Diels-Alder reaction of **5** with **26** in toluene[16] occurred in similar regio- and stereoselective manners as those observed for the total synthesis of **3**, affording the mixture of 2',4'-di-*O*-acetyl-con-nogarol (**27**) and 2',4'-di-*O*-acetyl-7,9-di-*epi*-con-nogarol (**28**) (**27**:**28** = 1:3) after air oxidation of the adducts during mild acidic work-up. Similarly to the reaction of **5** with **16**, preferential reaction of **5** with (7*S*,9*S*)-**26** through the transition state (**Ca**) may account for the observed diastereoselectivity.[16] In contrast to other known examples of the similar Diels-Alder reactions, the corresponding C_6-methyl ethers could not be detected although the methoxy(trimethylsilyloxy)diene (**26**) was employed as a diene.[3,17] Without separation of **27** and **28**, stereoselective introduction of the C_7-methoxy group was attempted according to the reported procedure.[19] Thus, reaction of the mixture of **27** and **28** with trifluoroacetic acid followed by the treatment with sodium methoxide yielded the mixture of (+)-2',4'-di-*O*-acetyl-7-con-*O*-methylnogarol (**29**) and (+)-2',4'-di-*O*-acetyl-7,9-di-*epi*-7-con-*O*-methylnogarol (**30**) (**29**:**30** = 1:3). This could be readily separated by TLC, **29**: mp 180-182 °C; $[\alpha]_D^{20}$ +308° (c 0.120, $CHCl_3$), and **30**: mp 217-219 °C; $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$). Synthetic **29** was shown to be identical with the authentic sample independently prepared from natural **2** by our hands, in all respects (mp, mmp, 400 MHz ^1H NMR, IR, MS). Both the acetates (**29** and **30**) were deprotected, affording natural (+)-7-con-*O*-methylnogarol (**2**), mp 250-254 °C (decomp.) and $[\alpha]_D^{20}$ +867° (c 0.045,

$CHCl_3$), and (+)-7,9-di-*epi*-7-con-*O*-methylnogarol (**31**), mp 213-216 °C (decomp.) and $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$), respectively. Synthetic **2** was identical with an authentic sample of natural **2** in all respects (mp, mmp, optical rotations, 400 MHz ^1H NMR, IR, MS).

Conclusion

As described above, the first total syntheses of **2-4** and their related compounds were accomplished by featuring the regioselective Diels-Alder reactions of **5**, the CDEF-ring system of nogalamycin congeners, with the various functionalized dienes (**8**, **16**, and **26**) as key steps. It appears evident that the explored synthetic scheme is highly promising as one of the most convenient and flexible synthetic routes to various structural types of nogalamycin congener. With completion of the total synthesis, *in vitro* cytotoxicity and *in vivo* antitumor activity assay were carried out on various structural types of nogalamycin congeners and their partial structures in order to disclose novel aspects of the structure-activity relationships. This is the subject of the accompanying paper.[20]

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a Horiba SEPA-200 automatic digital polarimeter. IR spectra measurements were performed with a JASCO A-200 IR spectrometer. ^1H NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM 400 spectrometer (400 MHz). All signals are expressed as ppm down field from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Assignments of peaks are indicated according to the numbering of IUPAC nomenclature to avoid confusion. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Unless otherwise noted, all reactions were performed using anhydrous solvents. Especially, tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl were used. Wako Gel C-200 and Merck Silica Gel $60F_{254}$ were used as an adsorbent for column chromatography and preparative thin layer chromatography (PTLC), respectively. The following abbrevations are used for solvents and reagents: acetic anhydride (Ac_2O), dl-10-camphorsulfonic acid (CSA), chloroform ($CHCl_3$), ethanol (EtOH), ethyl acetate (AcOEt), methanol (MeOH), tetrahydrofuran (THF), trimethylsilyl chloride (TMSCl).

Ethyl 2,6-Dimethyl-1,3-cyclohexadiene-1-carboxylate (6). Methylmagnesium bromide (45 ml, 3.0M ethereal solution, 0.14 mol) was added to a solution of dl-ethyl 2-methyl-4-oxo-2-cyclohexene-1-carboxylate (Hagemann's ester) (15 g, 82 mmol) in a mixture of THF (70 ml) and hexane (80 ml) in an ice bath with stirring under an argon atmosphere. After stirring for 30 min, the reaction was quenched by the addition of EtOH (20 ml) and the mixture was diluted with AcOEt. The ethyl acetate solution was washed successively with 1M HCl and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in benzene (150 ml) and CSA (1.0 g) was added to the benzene solution at room temperature. The reaction mixture was heated at reflux for 12 h. After being cooled to ambient temperature, the mixture was diluted with AcOEt. The ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, AcOEt-hexane), afforded pure **6** as a pale yellow caramel (8.0 g, 54%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7 Hz, $CO_2CH_2\underline{Me}$), 1.86 (3H, s, C_2-Me), 2.13 (3H, t, J = 2 Hz, C_4-Me), 1.7-2.7 (4H, m, C_5-H_2, C_6-H_2), 4.19 (2H, q, J

= 7 Hz, CO_2CH_2Me), 5.66 (1H, brs, W_H = 4 Hz, C_3-H) [lit. ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7Hz), 1.86 (3H, s), 2.13 (3H, s), 4.20 (2H, q, J = 7 Hz), 5.68 (1H, s, W_H = 4 Hz)[4]].

2,4-Dimethyl-1,3-cyclohexadiene-1-carboxylic Acid (7). The ethyl ester (**6**) (0.40 g, 2.2 mmol) was added to a solution of $AlBr_3$ (1.9 g, 7.0 mmol) in tetrahydrothiophene (5.0 ml) in an ice bath under an argon atmosphere. After stirring for 4.5 h at room temperature, the reaction mixture was poured onto 3M HCl and extracted with AcOEt. The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-hexane) to give pure **7** as pale yellow crystals (0.23 g, 67%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.87 (3H, s, C_2-Me), 2.19 (3H, t, J = 2 Hz, C_4-Me), 1.9-2.7 (4H, m, C_5-H_2, C_6-H_2), 5.70 (1H, brs, W_H = 5 Hz, C_3-H); IR (KBr) 3450, 1670, 1640, 1570, 1435, 1280, 1230, 940, 840, 545 cm^{-1}; MS m/z 152 (M^+), 137, 107. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%. Found: C, 70.90; H, 7.79%.

4-Bis(trimethylsilyloxy)methylene-1-methyl-3-methylene-1-cyclohexene (8). Butyllithium (0.67 ml, 1.5M hexane solution, 1.0 mmol) was added to a solution of diisopropylamine (0.12 g, 1.2 mmol) in THF (0.50 ml) cooled at -40 °C under an argon atmosphere. After stirring for 10 min at the same temperature, the solution was cooled at -78 °C. A solution of **7** (76 mg, 0.50 mmol) in THF (0.50 ml) and TMSCl (0.27 g, 2.5 mmol) were successively added and the reaction mixture was warmed up to room temperature. After stirring for 30 min at room temperature, the mixture was concentrated *in vacuo*. The residue was diluted with hexane and the hexane suspension was kept standing at room temperature. A supernatant of the suspension was taken out by a syringe and concentrated *in vacuo* to give **8** as a pale yellow caramel. ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.16 and 0.22 (18H, two s, $SiMe_3$ x 2), 1.76 (3H, s, C_1-Me), 1.9-2.5 (4H, m, C_5-H_2, C_6-H_2), 4.87 and 5.21 (2H, d, each J = 3 Hz, C_3=CH_2), 5.83 (1H, brs, C_2-H). Since this compound was found to be unstable to moisture, it was directly used for the next step without further purification.

(2R,3S,4R,5R,6R)-(+)-3,5-Diacetoxy-4-dimethylamino-8,10-dihydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12-hexahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-2',4'-Di-*O*-acetyl-7,8-dihydronogarene] (9). A solution of **5** (50 mg, 0.11 mmol) in THF (3.0 ml) was added to a solution of **8** [prepared from **7** (76 mg, 0.50 mmol) according to the procedure described above] in THF (1.0 ml) at room temperature under an argon atmosphere. After stirring for 30 min, 3M HCl (5.0 ml) was added and the mixture was stirred for 10 min on exposure to air. After addition of water and AcOEt, the mixture was neutralized to pH 8 with saturated aqueous $NaHCO_3$. The upper organic layer was separated and the lower aqueous layer was further extracted with AcOEt. The combined extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave a crude product, which was separated by column chromatography (SiO_2, AcOEt-hexane) to afford pure **9** as an orange solid (55 mg, 85% from **5**). Recrystallization from EtOH-hexane gave an analytical sample of **9** as orange crystals, mp 171-172 °C and $[\alpha]_D^{20}$ +468° (c 0.112, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, s, C_6-Me), 1.99 (3H, brs, C_{13}-Me), 2.13 and 2.16 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.20-2.52 (2H, m, C_{12}-H_2), 2.69 (1H, t, J = 10.8 Hz, C_4-H), 2.81-3.12 (2H, m, C_{11}-H_2), 5.13 (1H, d, J = 10.8 Hz, C_5-H), 5.21 (1H, dd, J = 4.0 and 10.8 Hz, C_3-H), 5.88 (1H, d, J = 4.0 Hz, C_2-H), 6.32 (1H, brs, C_{14}-H), 7.02 and 7.44 (2H, two s, C_7-H, C_{15}-H), 12.26 and 12.53 (2H, two s, OH x 2); IR (KBr) 3460, 1750, 1620, 1220, 1040 cm^{-1}; MS m/z 577 (M^+), 518, 517. *Anal.* Calcd. for $C_{31}H_{31}NO_{10}$: C, 63.46; H, 5.50; N, 2.39%. Found: C, 63.75; H, 5.40; N, 2.32%.

(2R,3S,4R,5R,6R)-(+)-4-Dimethylamino-3,5,8,10-tetrahydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12-hexahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-7,8-Dihydronogarene] (10). A suspension of **9** (12 mg, 21 μmol) in 1M HCl was heated at reflux for 15 h. After being cooled to 0 °C, the mixture was neutralized to pH 8 with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was separated by column chromatography (SiO_2, MeOH-AcOEt) to give pure **10** as an orange solid (9.0 mg, 88%). Recrystallization from EtOH-hexane gave an analytical sample of **10** as orange crystals, mp 251-257 °C and $[\alpha]_D^{20}$ +571° (c 0.070, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.74 (3H, s, C_6-Me), 2.01 (3H, s, C_{13}-Me), 2.21-2.50 (2H, m, C_{12}-H_2), 2.51 (6H, s, NMe_2), 2.68-3.02 (3H, m, C_4-H, C_{11}-H_2), 3.57 (1H, d, J = 10.5 Hz, C_5-H), 4.14 (1H, dd, J = 3.5 and 10.5 Hz, C_3-H), 5.90 (1H, d, J = 3.5 Hz, C_2-H), 5.92 (1H, s, C_{14}-H), 6.49 and 7.22 (2H, two s, C_7-H, C_{15}-H); IR (KBr) 3450, 1665, 1640, 1615 cm^{-1}. *Anal.* Calcd. for $C_{27}H_{27}NO_8 \cdot 0.5H_2O$: C, 64.53; H, 5.62; N, 2.79%. Found: C, 64.30; H, 5.57; N, 2.62%.

(2R,3S,4R,5R,6R)-(+)-3,5-Diacetoxy-4-dimethylamino-8,10-dihydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-2',4'-Di-*O*-acetylnogarene] (11).

a) Preparation of Synthetic 11 from 9. A solution of **9** (10 mg, 17 μmol), CSA (15 mg, 65 μmol), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (60 mg, 0.26 mmol) in benzene (5.0 ml) was heated at reflux for 5 h. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was chromatographed (SiO_2, AcOEt-hexane) to afford pure **11** as an orange solid (8.5 mg, 85%). Recrystallization from EtOH-hexane gave orange crystals, mp 177-179 °C and $[\alpha]_D^{20}$ +445° (c 0.062, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (3H, s, C_6-Me), 2.15 and 2.20 (6H, two s, COMe x 2), 2.29 (6H, s, NMe_2), 2.59 (3H, s, C_{13}-Me), 2.72 (1H, t, J = 10.8 Hz, C_4-H), 5.15 (1H, d, J = 10.8 Hz, C_5-H), 5.24 (1H, dd, J = 4.0 and 10.8 Hz, C_3-H), 5.92 (1H, d, J = 4.0 Hz, C_2-H), 7.06 (1H, s, C_7-H or C_{15}-H), 7.52 (1H, dd, J = 1.6 and 8.5 Hz, C_{12}-H), 7.77 (1H, brs, C_{14}-H), 8.19 (1H, s, C_7-H or C_{15}-H), 8.41 (1H, d, J = 8.5 Hz, C_{11}-H), 12.65 and 13.73 (2H, two s, ArOH x 2); IR (KBr) 3450, 1750, 1620, 1450, 1220, 1040 cm^{-1}; MS m/z 575 (M^+), 515. *Anal.* Calcd. for $C_{31}H_{29}NO_{11}$: C, 64.69; H, 5.08; N, 2.43%. Found: C, 64.50; H, 5.10; N, 2.32%. This sample was identical with authentic **11** prepared from natural **4** [see b)], on the basis of spectral (400 MHz ^1H NMR, IR, MS) and chromatographic (TLC) comparisons and mixed melting point measurement, mmp 176-179 °C.

b) Preparation of Authentic 11 from Natural 4. Ac_2O (0.22 g, 2.2 mmol) was added to a solution of a crude sample of natural **4**, mp 215-228 °C and $[\alpha]_D^{20}$ +896° (c 0.094, $CHCl_3$), (7.0 mg, 14 μmol) in EtOH (1.0 ml) at room temperature. After stirring for 1 h at room temperature, the mixture was concentrated *in vacuo* and the residue was separated by column chromatography (SiO_2, AcOEt-hexane) to give pure **11** as an orange solid (6.4 mg, 79%). Recrystallization from EtOH-hexane afforded an authentic sample of **11** as orange crystals, mp 176-178 °C and $[\alpha]_D^{20}$ +456° (c 0.064, $CHCl_3$).

(2R,3S,4R,5R,6R)-(+)-4-Dimethylamino-3,5,8,10-tetrahydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,-tetrahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-Nogarene] (4).

a) Preparation of 4 from Synthetic 11. Acidic hydrolysis of **11** (7.0 mg, 12 μmol) in the same manner to that described for **9**, followed by purification by column chromatography (SiO_2, MeOH-$CHCl_3$), gave pure **4** as an orange solid (5.2 mg, 87%). Recrystallization from EtOH afforded orange crystals, mp 277-281 °C (decomp.) and $[\alpha]_D^{20}$ +946° (c 0.070, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.78 (3H, s, C_6-Me), 2.56 (6H, s, NMe_2), 2.60 (3H, s, C_{13}-Me), 2.93 (1H, t, J = 10.5 Hz, C_4-

H), 3.62 (1H, d, J = 10.5 Hz, C_5-H), 4.19 (1H, dd, J = 3.5 and 10.5 Hz, C_3-H), 5.96 (1H, d, J = 3.5 Hz, C_2-H), 7.10, 7.26, and 7.29 (3H, three s, C_7-H, C_{14}-H, C_{15}-H), 7.50 and 8.27 (2H, two d, each J = 8.4 Hz, C_{11}-H, C_{12}-H); IR (KBr) 3440, 1660, 1610, 1450, 1385, 1280, 1220 cm^{-1}; MS m/z 491 (M^+), 404, 387, 375, 348. This sample showed no depression on mixed melting point measurement with authentic **4** [see b)], mmp 276-279 °C (decomp.). The spectral (400 MHz ^1H NMR, IR, MS) and chromatographic (TLC) behavior of this sample were identical with those of authentic **4** [see b)].

b) Purification of Authentic 4. A crude sample of natural **4**, mp 215-218 °C and $[\alpha]_D^{20}$ +896° (c 0.094, $CHCl_3$), was dissolved in $CHCl_3$ and the chloroform solution was filtered and concentrated *in vacuo*. Recrystallization of the residual solid from EtOH-hexane was repeated three times to afford a pure sample of authentic **4** as orange crystals, mp 276-279 °C and $[\alpha]_D^{20}$ +970° (c 0.100, $CHCl_3$).

dl-Ethyl 3,4-Epoxy-2,4-dimethyl-1-cyclohexene-1-carboxylate (12). 3-Chloroperbenzoic acid (*m*CPBA) (0.70 g, 80%, 3.3 mmol) was added to a solution of **6** (0.50 g, 2.8 mmol) in toluene (10 ml) in an ice bath. After stirring for 2 h, the reaction was quenched by the addition of saturated aqueous Na_2SO_3 and the mixture was extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt-hexane) of the residue gave pure **12** as a colorless caramel (0.27 g, 50%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7 Hz, $CO_2CH_2\underline{Me}$), 1.45 (3H, s, C_4-Me), 1.4-1.9 (2H, m, C_5-H_2), 1.9-2.7 (5H, m, C_2-Me, C_6-H_2), 3.01 (1H, s, C_3-H), 4.19 (2H, q, J = 7 Hz, $CO_2\underline{CH_2}Me$); IR (neat) 1705, 1275, 1260, 1230, 1195, 1070, 820 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%. Found: C, 67.05; H, 8.48%.

dl-4-Hydroxy-2,4-dimethyl-1-cyclohexene-1-methanol (13). Lithium triethylborohydride (Superhydride®) (6.0 ml, 1.0M THF solution, 6.0 mmol) was added to a solution of **12** (0.27 g, 1.4 mmol) in THF (5.0 ml) in an ice bath under an argon atmosphere. After stirring for 2 h at room temperature, the reaction was quenched by the addition of 1M HCl and the mixture was extracted with AcOEt. The ethyl acetate extracts were combined, washed with brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, AcOEt-hexane), afforded pure **13** as a colorless caramel (0.19 g, 87%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.26 (3H, s, C_4-Me), 1.70 (3H, brs, C_2-Me), 1.4-1.8 (2H, m, C_5-H_2), 1.8-2.4 (4H, m, C_3-H_2, C_6-H_2), 4.17 (2H, brs, $C\underline{H_2}OH$), 4.39 (1H, brs, OH); IR (neat) 3380, 1370, 1105, 995, 910 cm^{-1}; MS m/z 157 (M^+H), 156 (M^+), 141, 123, 111; High-resolution MS (M^+) 156.1156 (156.1149 calcd. for $C_9H_{16}O_2$).

dl-4-Hydroxy-2,4-dimethyl-1-cyclohexene-1-carbaldehyde (14). Active MnO_2 (2.9 g, 33 mmol) was added to a solution of **13** (0.29 g, 1.8 mmol) in a mixture of THF (5.0 ml) and hexane (30 ml) at room temperature. After stirring for 2 h at the same temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, AcOEt), affording pure **14** as a colorless caramel (0.25 g, 88%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, s, C_4-Me), 1.3-1.8 (3H, m, C_5-H_2, OH), 2.15 (3H, s, C_2-Me), 2.2-2.5 (4H, m, C_3-H_2, C_6-H_2), 10.17 (1H, s, CHO); IR (neat) 3430, 1665, 1630, 1400, 1380, 1250, 1110 cm^{-1}; MS m/z 154 (M^+), 124, 109; High-resolution MS (M^+) 154.0993 (154.1001 calcd. for $C_9H_{14}O_2$).

dl-4-Hydroxy-2,4-dimethyl-1-cyclohexene-1-carboxylic Acid (15). An aqueous solution (6.0 ml) of $NaClO_2$ (0.60 g, 6.6 mmol) and NaH_2PO_4 (0.60 g, 5.0 mmol) was added to a solution of **14** (0.14 g, 0.89 mmol) in a mixture of *tert*-butyl alcohol (15 ml) and 2-methyl-2-butene (4.0 ml) cooled at 0 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was diluted with brine, neutralized to pH 2 with 3M HCl, and extracted with ether. The ethereal extracts were combin-

ed, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt) to give pure **15** as a colorless solid (0.12 g, 75%). Recrystallization from ether-hexane gave an analytical sample of **15** as colorless crystals, mp 108-109 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.27 (3H, s, C_4-Me), 1.4-1.9 (3H, m, C_5-H_2, OH), 2.08 (3H, s, C_2-Me), 2.27 (2H, brs, C_3-H_2), 2.3-2.6 (2H, m, C_6-H_2), 6.30 (1H, brs, CO_2H); IR (KBr) 3430, 1670, 1635, 1405, 1270, 1240, 1190, 1110, 915 cm^{-1}; MS m/z 170 (M^+), 152, 124, 109. *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29%. Found: C, 63.58; H, 8.22%.

dl-1-Bis(trimethylsilyoxy)methylene-4-methyl-2-methylene-4-(trimethylsilyloxy)-cyclohexane (16). Butyllithium (1.2 ml, 1.5M hexane solution, 1.8 mmol) was added to a solution of diisopropylamine (0.24 g, 2.4 mmol) in THF (0.60 ml) cooled at -78 °C under an argon atmosphere. After stirring for 20 min at the same temperature, a solution of **15** (0.10 g, 0.60 mmol) in THF (1.2 ml) and TMSCl (0.39 g, 3.6 mmol) were successively added and the reaction mixture was warmed up to room temperature. After stirring was continued for 30 min at room temperature, the mixture was concentrated *in vacuo*. The residue was diluted with hexane and the hexane suspension was kept standing at room temperature. A supernatant of the suspension was taken out by a syringe and concentrated *in vacuo* to give **16** as a pale yellow caramel. ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.11, 0.15, and 0.21 (27H, three s, $SiMe_3$ x 3), 1.21 (3H, s, C_4-Me), 1.5-1.7 (2H, m, C_5-H_2), 1.8-2.5 (4H, m, C_3-H_2, C_6-H_2), 4.8-5.1 (2H, m, C_2=CH_2). Since this compound was found to be unstable to moisture, it was directly used for the next step without further purification.

(2R,3S,4R,5R,6R,13S)-(+)-3,5-Diacetoxy-4-dimethylamino-8,10,13-trihydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-2',4'-Di-*O*-acetyl-7-deoxynogarol] (17) and Its (2R,3S,4R,5R,6R,13R)-(+)-Isomer [(+)-2',4'-Di-*O*-acetyl-9-*epi*-7-deoxynogarol] (18).

a) Preparation of Synthetic 17 and 18 from 5 and 16. The diene (**16**) prepared from **15** (0.15 g, 0.90 mmol) according to the procedure described above, was dissolved in THF (1.8 ml). A 0.60 ml portion of the tetrahydrofuran solution of **16** was added to a solution of **5** (0.14 g, 0.30 mmol) heated at 60 °C under an argon atmosphere. Further two 0.60 ml portions of the solution of **16** were added to the reaction mixture after 0.5 and 1 hs' reactions, respectively, and heating at 60 °C was continued for total 2.5 h. After cooling to room temperature, 3M HCl (3.0 ml) was added and the mixture was stirred for 15 min on exposure to air. After addition of AcOEt and water, the mixture was neutralized to pH 8 with saturated aqueous $NaHCO_3$. The upper organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt-$CHCl_3$) of the residue gave a mixture of **17** and **18**, which was further separated by PTLC (SiO_2, AcOEt-$CHCl_3$) to afford pure **17** as an orange solid (25 mg, 14% from **5**) and pure **18** as an orange solid (90 mg, 50% from **5**).

17: Recrystallization from EtOH-hexane gave orange crystals, mp 268-271 °C (decomp.) and $[\alpha]_D^{20}$ +390° (0.155, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s, C_{13}-Me), 1.61 (3H, s, C_6-Me), 1.78-1.87 and 1.95-2.03 (2H, two m, C_{12}-H_2), 2.14 and 2.17 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.68 (1H, t, J = 10.8 Hz, C_4-H), 2.90-2.97 (4H, m, C_{11}-H_2, C_{14}-H_2), 5.13 (1H, d, J = 10.8 Hz, C_5-H), 5.22 (1H, dd, J = 3.9 and 10.8 Hz, C_3-H), 5.89 (1H, d, J = 3.9 Hz, C_2-H), 7.04 and 7.52 (2H, two s, C_7-H, C_{15}-H), 12.37 and 12.49 (2H, two s, ArOH x 2); IR (neat) 3520, 1750, 1670, 1620, 1460, 1415, 1385, 1220, 1040 cm^{-1}; MS m/z 595 (M^+), 536, 535, 494. This sample was identical with authentic **17** prepared from natural **3** [see b)], on the basis of spectral (400 MHz ^{1}H NMR, IR, MS) and chromatographic (TLC) comparisons and mixed melting point measurement, mmp 257-264 °C (decomp.).

18: Recrystallization from EtOH-hexane gave orange crystals, mp 182-184 °C and $[\alpha]_D^{20}$ +327° (c 0.102, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s, C_{13}-Me), 1.60 (3H, s, C_6-Me), 1.78-1.87 and 1.95-2.02 (2H, two m, C_{12}-H_2), 2.14 and 2.17 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.70 (1H, t, J = 10.7 Hz, C_4-H), 2.90-3.00 (4H, m, C_{11}-H_2, C_{14}-H_2), 5.13 (1H, d, J = 10.7 Hz, C_5-H), 5.22 (1H, dd, J = 3.9 and 10.7 Hz, C_3-H), 5.89 (1H, d, J = 3.9 Hz, C_2-H), 7.04 and 7.52 (2H, two s, C_7-H, C_{15}-H), 12.37 and 12.48 (2H, two s, ArOH x 2); IR (KBr) 3520, 1750, 1670, 1620, 1460, 1415, 1385, 1220, 1040 cm^{-1}; MS m/z 595 (M^+), 536, 535, 494; High-resolution MS (M^+) 595.2051 (595.2080 calcd. for $C_{31}H_{33}NO_{11}$).

b) Preparation of Authentic 17 from Natural 3. A crude sample of natural **3**, mp 190-210 °C, (5.0 mg, 10 μmol) and Ac_2O (1.0 g, 9.9 mmol) were dissolved in MeOH (2.0 ml). The methanolic solution was stirred for 1 h at room temperature and concentrated *in vacuo*. The residue was chromatogarphed (SiO_2, AcOEt-$CHCl_3$) to give a pure sample of authentic **17** as orange crystals (3.1 mg, 53%), mp 268-270 °C (decomp.) and $[\alpha]_D^{20}$ +408° (c 0.075, $CHCl_3$).

(2R,3S,4R,5R,6R,13S)-(+)-4-Dimethylamino-3,5,8,10,13-pentahydroxy-6.13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-7-Deoxynogarol] (3).

a) Preparation of 3 from Synthetic 17. Anhydrous K_2CO_3 (0.10 g, 0.72 mmol) was added to a solution of **17** (7.0 mg, 12 μmol) in MeOH (3.0 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at 50 °C for 20 min and cooled to ambient temperature. Oxalic acid was added to the reaction mixture until the color changed from purple to orange. The mixture was diluted with water and chloroform, and neutralized to pH 8 with saturated $NaHCO_3$. The lower chloroform layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, EtOH-$CHCl_3$) to afford a crude solid. This was recrystallized from $CHCl_3$-hexane to afford pure **3** as orange crystals (4.5 mg, 75%), mp 215-218 °C (decomp.) and $[\alpha]_D^{20}$ +1090° (c 0.100, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.47 (3H, s, C_{13}-Me), 1.74 (3H, s, C_6-Me), 1.80-1.90 and 1.95-2.03 (2H, two m, C_{12}-H_2), 2.53 (6H, s, NMe_2), 2.60 and 2.77 (2H, two d, J = 18.0 Hz, C_{14}-H_2), 2.75-2.84 (1H, m, C_{11}-H), 2.86 (1H, t, J = 10.8 Hz, C_4-H), 2.93-3.02 (1H, m, C_{11}-H), 3.57 (1H, d, J = 10.8 Hz, C_5-H), 4.16 (1H, dd, J = 3.5 and 10.8 Hz, C_3-H), 5.91 (1H, d, J = 3.5 Hz, C_2-H), 6.61 and 7.22 (2H, two s, C_7-H, C_{15}-H); IR (KBr) 3460, 1660, 1620, 1570, 1450, 1415, 1390, 1290, 1225, 1110, 1050, 1005, 780 cm^{-1}; MS m/z 511 (M^+), 424. This sample showed no depression on mixed melting measurement with authentic **3** prepared from natural **3** [see b)], mmp 216-220 °C (decomp.). The spectral (400 MHz ^1H NMR, IR, MS) and chromatographic (TLC) behavior of this sample were identical with those of authentic **3** [see b)].

b) Purification of Authentic 3. A crude sample of natural **3**, mp 190-210 °C, was purified sequentially by column chromatography (SiO_2, EtOH-$CHCl_3$) and recrystallization from EtOH-hexane to give a pure sample of authentic **3** as orange crystals, mp 219-222 °C (decomp.) and $[\alpha]_D^{20}$ +1150° (c 0.110, $CHCl_3$).

(2R,3S,4R,5R,6R,13R)-(+)-4-Dimethylamino-3,5,8,10,13-pentahydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-9-*epi*-7-Deoxynogarol] (19). The same transesterification of **18** (20 mg, 34 μmol) as that described for **17** gave crude **19** after concentration of the chloroform solution *in vacuo*. This was purified by column chroamtography (SiO_2, EtOH-$CHCl_3$) to give **19** as orange crystals (11 mg, 64%), mp 215-217 °C and $[\alpha]_D^{20}$ +413° (c 0.135, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.38 (3H, s, C_{13}-Me), 1.70 (3H, s, C_6-Me), 1.65-1.74 and 1.98-2.06 (2H, two m, C_{12}-H_2), 2.57 (6H, s, NMe_2), 2.73-2.96 (5H, m, C_4-H, C_{11}-H_2, C_{14}-H_2), 3.58 (1H, d, J = 10.7 Hz, C_5-H), 4.17 (1H, dd, J = 3.6 and 10.7 Hz, C_3-H), 5.83 (1H, d, J = 3.6 Hz, C_2-H), 6.78 and 7.21 (2H, two s,

C_7-H, C_{15}-H); IR (KBr) 3460, 1660, 1620, 1570, 1450, 1415, 1390, 1290, 1225, 1110, 1050, 1005, 780 cm^{-1}; MS m/z 511 (M^+), 424. *Anal.* Calcd. for $C_{27}H_{29}NO_9 \cdot H_2O$: C, 61.23; H, 5.90; N, 2.65%. Found: C, 61.50; H, 5.65; N, 2.56%.

Dimethyl 3-Hydroxy-3-methylglutarate (20). Addition reaction of allylmagnesium bromide to AcOEt (87%),[13] followed by sequential ozonolysis of the two double bonds of 4-methyl-1,6-heptadien-4-ol and esterification of 4-hydroxy-4-methylglutaric acid with diazomethane (92%, 2 steps),[13] afforded **20**. ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (3H, s, C_3-Me), 2.69 (4H, s, C_2-H_2, C_4-H_2), 3.74 (6H, s, CO_2Me x 2), 4.05 (1H, s, OH).

dl-*tert*-Butyl 2-*tert*-Butoxycarbonyl-5-hydroxy-5-methyl-3-oxo-1-cyclohexene-1-acetate (21). *tert*-Butyl lithioacetate (11 g, 95 mmol)[21] was added to a stirred solution of **20** (1.9 g, 10 mmol) in THF (60 ml) cooled at -78 °C under an argon atmosphere. The reaction mixture was allowed to warm up to ambient temperature and stirring was continued for 4 h. The mixture was diluted with AcOEt and the ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in MeOH (100 ml). Calcium acetate monohydrate (20 g, 0.16 mol) was added to the methanolic solution at room temperature, and the reaction mixture was stirred for 10 h and concentrated *in vacuo*. The residue was diluted with AcOEt. The ethyl acetate solution was washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, AcOEt-hexane), gave crude **21** as a pale yellow solid. This was triturated with ether to yield pure **21** as colorless crystals (1.7 g, 50%), mp 107-198 °C. ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (3H, s, C_5-Me), 1,47 and 1.53 (18H, two s, $CO_2{}^tBu$ x 2), 1.99 (1H, s, OH), 2.48 (1H, d, J =17 Hz, C_4-H), 2.66 (2H, brs, C_6-H_2), 2.70 (1H, d, J = 17 Hz, C_4-H), 3.25 (H, s, CH_2CO_2); IR (KBr) 3450, 1730, 1720, 1660, 1630, 1400, 1370, 1330, 1295, 1270, 1060, 1100 cm^{-1}; MS m/z 283 (M^+-^{t}Bu), 228, 211. *Anal.* Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29%. Found: C, 63.49; H, 8.42%.

dl-2,4-Dimethyl-4-hydroxy-6-oxo-1-cyclohexene-1-carboxylic Acid (22). A solution of **21** (6.0 g, 18 mmol) in formic acid (20 ml) was stirred at room temperature for 2 h and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-$CHCl_3$) to afford crude **22** as a pale yellow solid. Recrystallization from AcOEt-hexane have pure **22** as colorless crystals (1.7 g, 52%), mp 126-130 °C (decomp.). ^1H NMR (90 MHz, $CDCl_3$-CD_3COCD_3) δ 1.40 (3H, s, C_4-Me), 2.11 (1H, s, OH), 2.48 (3H, s, C_2-Me), 2.75 (2H, s, C_5-H_2), 2.87 (2H, s, C_3-H_2); IR (KBr) 3400, 3300, 1720, 1650, 1630, 1405, 1235, 1120, 745 cm^{-1}; MS m/z 184 (M^+), 166, 148. *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57%. Found: C, 58.53; H, 6.65%.

(4R*,6R*)-Methyl 4,6-Dihydroxy-2,4-dimethyl-1-cyclohexene-1-carboxylate (24) and Its (4R*,6S*)-Isomer (25). An aqueous solution (5.0 ml) of $NaBH_4$ (0.40 g, 11 mmol) was added to an aqueous solution (95 ml) of **22** (0.90 g, 4.9 mmol) and $CeCl_3 \cdot 7H_2O$ (45 g, 0.12 mol) with stirring at room temperature. After stirring for 5 min, the reaction mixture was diluted with THF and neutralized to pH 4 with saturated aqueous $NaHSO_4$. A ethereal solution of diazomethane was added to the mixture until the yellow color was maintained. The mixture was diluted with AcOEt and the upper organic layer was separated, washed with brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatogrphy (SiO_2, AcOEt-hexane), afforded pure **24** as a colorless caramel (0.31 g, 31%) and pure **25** as a colorless caramel (33 mg, 3%).

24: ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, s, C_4-Me), 1.70 (1H, dd, J = 4.6 and 14.4 Hz, $C_{5\text{-}ax}$-H), 2.15 (1H, dt, J = 14.4 and 2.1 Hz, $C_{5\text{-}eq}$-H), 2.30 (1H, d, J = 18.9 Hz, $C_{3\text{-}ax}$-H), 2.40 (1H, dd, J = 1.9 and 18.9 Hz, $C_{3\text{-}eq}$-H), 3.44 (1H, brd, J =

4.2 Hz, C_6-OH), 3.81 (3H, s, CO_2Me), 3.90 (1H, s, C_4-OH), 4.67 (1H, brs, C_6-H); IR (neat) 3420, 1710, 1640, 1430, 1250, 1155, 1095, 1040 cm^{-1}; MS m/z 182 (M^+-H_2O), 150; High-resolution MS (M^+-H_2O) 182.0939 (182.0941 calcd. for $C_{10}H_{14}O_3$).

25: ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (1H, s, C_4-OH), 1.35 (3H, s, C_4-Me), 1.68 (1H, dd, J = 8.2 and 13.3 Hz, C_{5-ax}-H), 2.14 (1H, ddd, J = 2.2, 6.2, and 13.3 Hz, C_{5-eq}-H), 2.20 (1H, d, J = 18.6 Hz, C_{3-ax}-H), 2.39 (1H, brd, J = 18.6 Hz, C_{3-eq}-H), 3.08 (1H, d, J = 3.7 Hz, C_6-OH), 3.80 (3H, s, CO_2Me), 4.78 (1H, m, C_6-H); IR (neat) 3420, 1705, 1430, 1260, 1095, 1045 cm^{-1}; MS m/z 182 (M^+-H_2O), 167, 150; High-resolution MS (M^+-H_2O) 182.0945 (192.0941 calcd. for $C_{10}H_{14}O_3$).

(1R*,5R*)-Methyl 1,3,3,7-tetramethyl-2,4-dioxabicyclo[3.3.1]non-6-ene-6-carboxylate (vi). A solution of **24** (20 mg, 0.10 mmol) and CSA (5.0 mg, 20 μmol) in 2,2-dimethoxypropane (5.0 ml) was heated at reflux for 10 min. After cooling, the reaction mixture was diluted with AcOEt and the ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo* followed by purification by column chromatography (SiO_2, AcOEt-hexane), afforded pure **vi** as a colorless caramel (8.0 mg, 33%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.23, 1.34, and 1.42 (9H, three s, C_4-Me, CMe_2), 2.07 (3H, s, C_2-Me), 2.1-2.5 (4H, m, C_3-H_2, C_5-H_2), 3.78 (3H, s, CO_2Me), 4.8-5.0 (1H, m, C_6-H); IR (neat) 1710, 1640, 1430, 1370, 1250, 1230, 1190, 1170, 1120, 1060 cm^{-1}; MS m/z 225 (M^+-Me), 165; High-resolution MS (M^+-Me) 224.9286 (224.9295 calcd. for $C_{12}H_{17}O_4$).

(4R*,6R*)-1-Methoxy(trimethylsilyloxy)methylene-4-methyl-2-methylene-4,6-bis-(trimethylsilyloxy)cyclohexane (26). Butyllithium (1.2 ml, 1.5M hexane solution, 1.9 mmol) was added to a solution of diisopropylamine (0.20 g, 2.0 mmol) in THF (1.0 ml) cooled at -78 °C under an argon atmosphere. After stirring for 15 min at the same temperature, a solution of **24** (0.13 g, 0.65 mmol) in THF (1.0 ml) and TMSCl (0.42 g, 3.9 mmol) were successively added and the reaction mixture was allowed to warm up to room temperature. After stirring for 30 min at room temperature, the mixture was concentrated *in vacuo*. The residue was diluted with hexane and the hexane suspension was kept standing at room temperature. A supernatant of the hexane suspension was taken out by a syringe and concentrated *in vacuo* to give **26** as a pale yellow caramel. ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (27H, s, $SiMe_3$ x 3), 1.20 (3H, s, C_4-Me), 1.9-2.0 (4H, m, C_3-H_2, C_5-H_2), 3.75 (3H, s, OMe), 5.05 and 5.65 (2H, two brs, C_2=CH_2), 6.75 (1H, brt, J = 4 Hz, C_6-H). Since this compound was found to be unstable to moisture, it was directly used for the next step without further purification.

(2R,3S,4R,5R,6R,11R,13R)-3,5-Diacetoxy-4-dimethylamino-8,10,11,13-tetrahydroxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]-oxocine-9,16-dione [2',4'-Di-*O*-acetyl-7-con-nogarol] (27) and Its (2R,3S,4R,6R,11S,13S)-Isomer [2',4'-Di-*O*-acetyl-7,9-di-*epi*-7-con-nogarol] (28). A solution of **5** (45 mg, 0.10 mmol) and **26** [prepared from **24** (0.13 g, 0.65 mmol) according to the procedure described above] in toluene (1.0 ml) was heated at 100 °C for 10 min under an argon atmosphere and cooled to ambient temperature. 3M HCl (1.0 ml) was added to the mixture and stirring was continued for 10 min on exposure to air. The mixture was diluted with AcOEt and neutralized to pH 8 with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, AcOEt-$CHCl_3$), gave a mixture of **27** and **28** (**27**:**28** = 1:3 by ^1H NMR) as an orange solid (28 mg, 45% from **5**). ^1H NMR (400 MHz, $CDCl_3$) δ (**27**) 1.46 (3H, s, C_{13}-Me), 1.60 (3H, s, C_6-Me), 1.98 (1H, dd, J = 5.0 and 14.7, C_{12-ax}-H), 2.14 and 2.17 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.37 (1H, dt, J = 14.7 and 2.0 Hz, C_{12-eq}-H), 2.68 (1H, t, J = 10.8 Hz, C_4-H), 2.88 (1H, d, J =

17.8 Hz, C_{14-ax}-H), 3.11 (1H, dd, J = 2.0 and 17.8 Hz, C_{14-eq}-H), 3.33 (1H, s, C_{13}-OH), 3.50 (1H, d, J = 4.2 Hz, C_{11}-OH), 5.14 (1H, d, J = 10.8 Hz, C_5-H), 5.22 (1H, dd, J = 3.9 and 10.8 Hz, C_3-H), 5.28-5.33 (1H, m, C_{11}-H), 5.90 (1H, d, J = 3.9 Hz, C_2-H), 7.06 and 7.61 (2H, two s, C_7-H, C_{15}-H), 12.40 and 12.63 (2H, two s, ArOH x 2), δ (**28**) 1.46 (3H, s, C_{13}-Me), 1.60 (3H, s, C_6-Me), 1.96 (1H, dd, J = 5.0 and 14.7 Hz, C_{12-ax}-H), 2.16 and 2.20 (6H, two s, COMe x 2), 2.30 (6H, s, NMe_2), 2.38 (1H, dt, J = 14.7 and 2.0 Hz, C_{12-eq}-H), 2.73 (1H, t, J = 10.8 Hz, C_4-H), 2.87 (1H, d, J = 17.8 Hz, C_{14-ax}-H), 3.17 (1H, dd, J = 2.0 and 17.8 Hz, C_{14-eq}-H), 3.49 (1H, s, C_{13}-OH), 3.53 (1H, d, J = 4.2 Hz, C_{11}-OH), 5.14 (1H, d, J = 10.8 Hz, C_5-H), 5.23 (1H, dd, J = 3.9 and 10.8 Hz, C_3-H), 5.28-5.33 (1H, m, C_{11}-H), 5.90 (1H, d, J = 3.9 Hz, C_2-H), 7.06 and 7.55 (2H, two s, C_7-H, C_{15}-H), 12.32 and 12.57 (2H, two s, ArOH x 2); IR (KBr) 3480, 1750, 1670, 1620, 1460, 1415, 1390, 1290, 1220, 1120, 1045 cm^{-1}; MS m/z 611 (M^+), 575, 515.

(2R,3S,4R,5R,6R,11R,13R)-(+)-3,5-Diacetoxy-4-dimethylamino-8,10,13-trihydroxy-11-methoxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno-[1,2-b]oxocine-9,16-dione [(+)-2',4'-Di-*O*-acetyl-7-con-*O*-methylnogarol] (29) and Its (2R,3S,4R,5R,6R,11S,13S)-(+)-Isomer [(+)-2',4'-Di-*O*-acetyl-7,9-di-*epi*-7-con-*O*-methylnogarol] (30).

a) Preparation of Synthetic 29 and 30 from the Mixture of 27 and 28. The mixture of **27** and **28** (28 mg, 46 μmol) was dissolved in trifluoroacetic acid (1.0 ml) cooled at 0 °C. After stirring for 3 h at the same temperature, sodium methoxide (2.0M MeOH solution) was added to the reaction mixture at 0 °C until the color changed from orange to purple, and stirring was further continued for 5 min. The mixture was diluted with AcOEt and 1M HCl, and neutralized to pH 8 with saturated aqueous $NaHCO_3$. The upper organic layer was separated, washed with brine, and dried (Na_2SO_4). Filtration and concentration *in vacuo*, followed by purification by column chromarography (SiO_2, AcOEt-$CHCl_3$), gave a mixture of **29** and **30** as a yellow solid (25 mg, 87%). This was separated by PTLC (SiO_2, AcOEt-$CHCl_3$) to give pure **29** as a yellow solid and pure **30** as a yellow solid.

29: Recrystallization from ether-hexane gave yellow crystals (3.5 mg, 12%), mp 180-182 °C and $[\alpha]_D^{20}$ +308° (0.120, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, s, C_{13}-Me), 1.60 (3H, s, C_6-Me), 1.75 (1H, dd, J = 3.8 and 14.8 Hz, C_{12-ax}-H), 2.14 and 2.18 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.48 (1H, dt, J =14.8 and 2.0 Hz, C_{12-eq}-H), 2.68 (1H, t, J = 10.8 Hz, C_4-H), 2.86 (1H, d, J = 18.1 Hz, C_{14-ax}-H), 3.19 (1H, dd, J = 2.0 and 18.1 Hz, C_{14-eq}-H), 3.61 (3H, s, OMe), 4.65 (1H, s, C_{13}-OH), 4.88 (1H, dd, J = 2.0 and 3.8 Hz, C_{11}-H), 5.14 (1H, d, J =10.8 Hz, C_5-H), 5.22 (1H, dd, J = 3.9 and 10.7 Hz, C_3-H), 5.89 (1H, d, J = 3.9 Hz, C_2-H), 7.05 and 7.59 (1H, two s, C_7-H, C_{15}-H), 12.44 and 12.60 (2H, two s, ArOH x 2); IR (KBr) 3490, 1750, 1670, 1620, 1450, 1415, 1385, 1290, 1220, 1040 cm^{-1}; MS m/z 625 (M^+), 575, 515. This sample showed no depression on mixed melting point measurement with authentic **29** prepared from natural **2** [see b)], mmp 180-182 °C. The spectral (400 MHz ^1H NMR, IR, MS) and chromatographic (TLC) behavior of this sample were identical with those of authentic **29** [see b)].

30: Recrystallization from ether-hexane have yellow crystals (10 mg, 35%), mp 217-219 °C (decomp.) and $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, s, C_{13}-Me), 1.63 (3H, s, C_6-Me), 1.75 (1H, dd, J = 3.7 and 14.8 Hz, C_{12-ax}-H), 2.15 and 2.17 (6H, two s, COMe x 2), 2.29 (6H, s, NMe_2), 2.48 (1H, dt, J = 14.8 and 2.0 Hz, C_{12-eq}-H), 2.68 (1H, t, J = 10.8 Hz, C_4-H), 2.88 (1H, d, J = 18.2 Hz, C_{14-ax}-H), 3.19 (1H, dd, J = 2.0 and 18.2 Hz, C_{14-eq}-H), 3.62 (3H, s, OMe), 4.64 (1H, s, C_{13}-OH), 4.87 (1H, dd, J = 2.0 and 3.7 Hz, C_{11}-H), 5.13 (1H, d, J = 10.8 Hz, C_5-H), 5.21 (1H, dd, J = 3.9 and 10.8 Hz, C_3-H), 5.89 (1H, d, J = 3.9 Hz, C_2-H), 7.05 and 7.57 (2H, two s, C_7-H, C_{15}-H), 12.43 and 12.59 (2H, two s, ArOH x

2); IR (KBr) 3490, 1750, 1620, 1450, 1415, 1385, 1290, 1220, 1040 cm^{-1}; MS m/z 625 (M^+), 575, 515; High-resolution MS (M^+) 625.2150 (625.2156 calcd. for $C_{32}H_{35}NO_{12}$).

b) Preparation of Authentic 29 from Natural 2. A crude sample of natural **2** (5.0 mg, 9.2 μmol) and Ac_2O (1.0 g, 9.8 mmol) was dissolved in $CHCl_3$ (1.0 ml). The chloroform solution was heated at reflux for 30 min, cooled to room temperature, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-$CHCl_3$) to give pure **29** as a yellow solid. Recrystallization from EtOH-hexane gave an authentic sample of **29** as yellow crystals (4.0 mg, 70%), mp 182-184 °C and $[\alpha]_D^{20}$ +272° (c 0.100, $CHCl_3$).

(2R,3S,4R,5R,6R,11R,13R)-(+)-4-Dimethylamino-3,5,8,10,13-pentahydroxy-11-methoxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-7-con-*O*-Methylnogarol] (2).

a) Preparation of 2 from Synthetic 29. Sodium methoxide (0.10 g, 1.9 mmol) was added to a solution of **29** (5.0 mg, 8.0 μmol) in MeOH (1.0 ml) at room temperature. The reaction mixture was heated at 50 °C for 10 min, cooled to ambient temperature, and neutralized to pH 8 with 3M HCl. The mixture was extracted with AcOEt, and the combined extracts were washed with brine and dried (Na_2SO_4). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, EtOH-$CHCl_3$), gave crude **2** as an orange solid. This was recrystallized from EtOH-hexane to yield pure **2** as orange crystals (4.0 mg, 92%), mp 250-254 °C (decomp.) and $[\alpha]_D^{20}$ +867° (c 0.045, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.45 (3H, s, C_{13}-Me), 1.84 (1H, dd, J = 3.7 and 14.7 Hz, C_{12-ax}-H), 2.49 (1H, brd, J = 14.7 Hz, C_{12-eq}-H), 2.54 (6H, s, NMe_2), 2.71 (1H, d, J = 18.3 Hz, C_{14-ax}-H), 2.85 (1H, brd, J = 18.3 Hz, C_{14-eq}-H), 2.90 (1H, t, J = 10.8 Hz, C_4-H), 3.59 (1H, d, J = 10.8 Hz, C_5-H), 3.60 (3H, s, OMe), 4.18 (1H, dd, J = 3.6 and 10.8 Hz, C_3-H), 4.84 (1H, dd, J = 1.8 and 3.7 Hz, C_{11}-H), 5.92 (1H, d, J = 3.6 Hz, C_2-H), 6.64 and 7.24 (2H, two s, C_7-H, C_{15}-H); IR (KBr) 3480, 1640, 1615, 1575, 1450, 1415, 1395, 1290, 1200, 1105, 1055, 1005, 780 cm^{-1}; MS m/z 541 (M^+), 491, 404. This sample was identical with authentic **2** prepared from natural **2** [see b)], on the basis of spectral (400 MHz ^1H NMR, IR, MS) and chromatographic (TLC) comparisons and mixed melting point measurement, mmp 249-252 °C (decomp.).

b) Purification of Authentic 2. A crude sample of natural **2** was purified sequentially by column chromatography (SiO_2, AcOEt-$CHCl_3$) and recrystallization from EtOH-hexane to give a pure sample of authentic **2** as orange crystals, mp 247-249 °C (decomp.) and $[\alpha]_D^{20}$ +857° (c 0.112, $CHCl_3$).

(2R,3S,4R,5R,6R,11S,13S)-(+)-4-Dimethylamino-3,5,8,10,13-pentahydroxy-11-methoxy-6,13-dimethyl-2,6-epoxy-3,4,5,6,11,12,13,14-octahydro-2H-naphthaceno[1,2-b]oxocine-9,16-dione [(+)-7,9-Di-*epi*-7-con-*O*-methylnogarol] (31). Transesterification of **30** (15 mg, 24 μmol) in the same manner as that described for **29** gave crude **30** as an orange solid after concentration of the ethyl acetate extracts *in vacuo*. This was purified sequentially by column chromatography (SiO_2, AcOEt-hexane) and recrystallization from EtOH-hexane to give pure **31** as orange crystals (10 mg, 77%), mp 213-216 °C (decomp.) and $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.41 (3H, s, C_{13}-Me), 1.64 (1H, dd, J = 3.8 and 14.7 Hz, C_{12-ax}-H), 1.73 (3H, s, C_6-Me), 2.45 (1H, brd, J = 14.7 Hz, C_{12-eq}-H), 2.51 (6H, s, NMe_2), 2.71 (1H, d, J = 17.8 Hz, C_{14-ax}-H), 2.73 (1H, t, J = 10.5 Hz, C_4-H), 2.99 (1H, brd, J = 17.8 Hz, C_{14-eq}-H), 3.56 (1H, d, J = 10.5 Hz, C_5-H), 3.66 (3H, s, OMe), 4.15 (1H, dd, J = 3.6 and 10.5 Hz, C_3-H), 4.75-4.80 (1H, m, C_{11}-H), 5.87 (1H, d, J = 3.6 Hz, C_2-H), 6.89 and 7.26 (2H, two s, C_7-H, C_{15}-H); IR (KBr) 3460, 1660, 1615, 1445, 1410, 1385, 1280, 1220, 1100, 1045, 1010, 780 cm^{-1}; MS m/z 541 (M^+), 491, 404; High-resolution MS (M^+) 541.1948 (541.1948 calcd. for $C_{28}H_{31}NO_{10}$).

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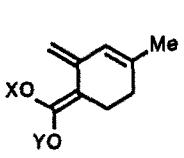
References and Notes

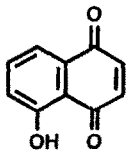
1) Parts of this series of reports have been the subjects of four preliminary communications: a) M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, **26**, 2693 (1985); b) *Idem, ibid.*, **27**, 2145 (1986); c) *Idem, ibid.*, **29**, 791 (1988); d) F. Matsuda, M. Kawasaki, M. Ohsaki, K. Yamada, and S. Terashima, *Chem. Lett.*, 653 (1988).

2) Parts 1 and 2: M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron*, the preceding papers.

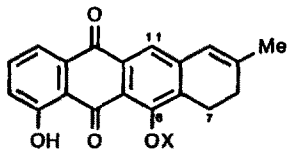
3) At the outset, the ethoxy(trimethylsilyloxy)diene (**i**) obtainable from **6** was anticipated to be one of the most suitable dienes, based on the results reported for 11-deoxyanthracyclinone synthesis.[4] However, it had been reported that the regioselective Diels-Alder reaction of **i** with juglone (**ii**) usually afforded the C_6-ethyl ether (**iv**) as a major product along with a small amount of the objective 11-deoxyanthracyclinone (**iii**).[4] Furthermore, the conditions required to effect cleavage of the ethyl ether was found to be too drastic to utilize **i** for the synthesis of **4**.[4] Accordingly, **8** was selected as the most favorable diene.



i X = Et, Y = TMS or
X = TMS, Y = Et



ii



X = H **iii**
X = Et **iv**

4) J-P. Gesson, J-C. Jacquesy, and B. Renoux, *Tetrahedron*, **40**, 4743 (1984).

5) M. Node, K. Nishide, M. Sai, K. Fuji, and E. Fujita, *J. Org. Chem.*, **46**, 1991 (1981).

6) Hydrolysis of **6** under acidic or basic conditions resulted in the formation of 2,4-dimethylbenzoic acid due to concomitant air oxidation.

7) A model study was first attempted employing juglone (**ii**) as a dienophile. Thus, the Diels-Alder reaction of **ii** with **8** was found to undergo in a completely regioselective manner to yield the 11-deoxyanthracyclinone (**iii**)[4] as a sole product [1) **ii**, **8**, THF, rt, 30 min 2) 3M HCl, rt, 10 min, 86%]. With this result in hand, the Diels-Alder reaction of **5** with **8** was examined.

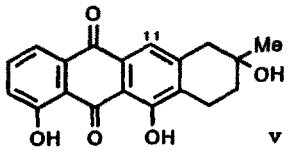
8) R.K. Boeckman, Jr., T.M. Dolak, and K.O. Culos, *J. Am. Chem. Soc.*, **100**, 7098 (1978).

9) Probably due to the oxidative removal of the $C_{3'}$-dimethylamino group, a low yield of **11** was only obtained in the absence of CSA. Protonation of the $C_{3'}$-dimethylamino group may avoid such oxidative cleavage.

10) Bromination of the benzylic C_7-position of **17** also afforded a complex mixture of the products.

11) J.G. Bauman, R.C. Hawley, and H. Rapoport, *J. Org. Chem.*, **50**, 1569 (1985).

12) Prior to the Diels-Alder reaction with **5**, a model study was performed employing **ii** as a dienophile. The regioselective Diels-Alder reaction of **ii** with



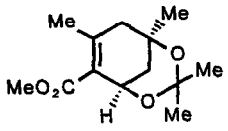
v

16 was found to give the dl-11-deoxyanthracyclinone (**v**) as a sole product [1) **ii**, **16**, THF, 60 °C, 2.5 h 2) 3M HCl, rt, 10 min, 33%].

13) R. Tschesche and H. Machleidt, *Liebigs Ann. Chem.*, **631**, 61 (1960).

14) M. Yamaguchi, *Yuki Gosei Kagaku Kyokai Shi*, **45**, 969 (1987).

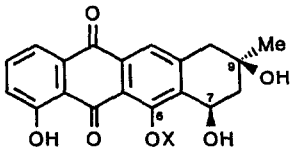
15) Both the *cis*- and *trans*-esters (**24** and **25**) were subjected to acetonide formation to determine their relative stereochemistries at the C_7- and C_9-positions. While reaction of **24** with 2,2-dimethoxypropane under acidic conditions readily produced the acetonide (**vi**), the same treatments of **25** resulted in a complete recovery of the starting material. These results unambiguously established the structures of **24** and **25** (see Experimental).



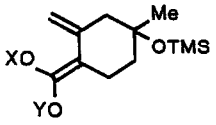
vi

16) Interestingly, when **5** was allowed to react with **26** under the same conditions as those employed for the total synthesis of **3** [1) **5**, **26**, THF, 60 °C, 20 min 2) 3M HCl, rt, 10 min], the Diels-Alder reaction was found to proceed sluggishly, resulting in highly diastereoselective formation of **28** (7%, **27**:**28** > 1:10). The diastereoselectivity more increased than that observed for the total synthesis of **3** can be also rationalized by considering the transition states (**Bb** and **Cb**). Thus, **Cb** in which (7R,9R)-**26** approaches to **5** is anticipated to be more sterically hindered than **Ca** due to both the C_7- and C_9-trimethylsilyloxy groups. The reason why the diastereoselectivity of the Diels-Alder reaction in toluene could be improved in favor of **27**, is probably due to the elevated reaction temperature.

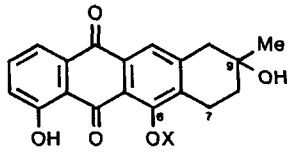
17) In contrast to the Diels-Alder reaction of **ii** with **i**,[3] the reaction of **ii** with **26** similarly afforded the 11-deoxyanthracyclinone (**vii**) as a sole product without any formation of its C_6-methyl ether (**viii**) [1) **ii**, **26**, THF, 60 °C, 2.5 h 2) 3M HCl, rt, 10 min, 17%]. On the other hand, the Diels-Alder reaction of **ii** with the methoxy(trimethylsilyloxy)diene (**ix**)[18] was found to produce a mixture of the 11-deoxyanthracyclinone (**v**) and its C_6-methyl ether (**x**) [1) **ii**, **ix**, THF, 60 °C, 2.5 h 2) 3M HCl, rt, 10 min, 10% (**v**), 12% (**x**)]. Accordingly, the specific formation of **27** and **28** from **5** and that of **vii** from **ii** in the Diels-Alder reactions utilizing **26** as a diene, may be due to the presence of additional oxygen functionality at the C_7-position.



X = H **vii**
X = Me **viii**



ix X = Me, Y = TMS or X = TMS, Y = Me



X = H **v**
X = Me **x**

18) The diene (**ix**) was prepared from **15** by the sequence (1) esterification with diazomethane (ether, rt, 97%) and (2) treatment of the dianion of the formed methyl ester with trimethylsilyl chloride (LDA, TMSCl, THF, -78 °C → rt, 30 min).

19) P.F. Wiley, D.W. Elrod, D.J. Houser, J.L. Johnson, L.M. Pshigoda, W.C. Krueger, and A. Moscowitz, *J. Org. Chem.*, **44**, 4030 (1979).

20) F. Matsuda, M. Kawasaki, M. Ohsaki, K. Yamada, and S. Terashima, *Tetrahedron*, the accompanying paper.

21) M.W. Rathke and D.F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973).