Synthetic Anthracyclines: Regiospecific Total Synthesis of a D-Ring Indole Analogue of Daunomycin

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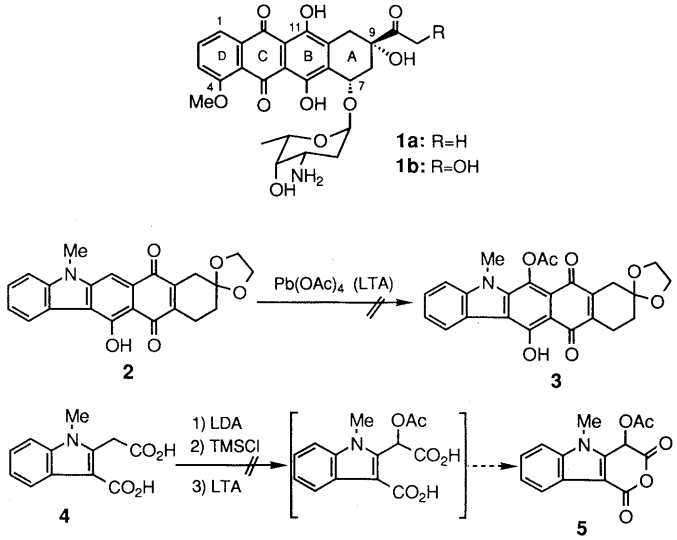
The 4-methoxy-5-methylpyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-dione (9), prepared from methyl 3-methoxycarbonyl-1-methylindol-2-yl acetate (6), underwent a strong base-induced cycloaddition reaction with 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (11) to give the tetrahydronaphtho[2,3-*b*]carbazole-7,12-dione (10), regioselectively. The cycloadduct (10) was successfully converted to a D-ring indole analogue of daunomycin (1a).

Keywords daunomycin analogue; heteroanthracycline; D-ring indole analogue; cycloaddition; antitumor agent

The anthracycline antibiotics, daunomycin (**1a**) and adriamycin (**1b**), are powerful antitumor agents which are widely used in the clinic to treat leukemia and solid tumors.[1,2] However, their utility is seriously restricted by various undesirable side effects, the most serious of which is dose-related cardiotoxicity.[3] It is suggested that the antitumor activity and cardiotoxicity are caused by some reactive oxygen species such as $O_2^{\cdot-}$, H_2O_2, and $OH^{\cdot}$, which are formed by a cyclic redox reaction of anthracyclines.[4] The C-ring quinone moiety of anthracyclines plays an important role in the redox reaction, and some derivatives modified in the C-ring of anthracyclines show antitumor activity with low cardiotoxicity.[5] The B and/or D-ring modification of the chromophore is also known to have some effect on the C-ring quinone moiety, because 11-deoxy-[6] and 4-demethoxyanthracyclines[6b,7] are well recognized to exhibit higher values of therapeutic index than natural anthracyclines. It would be interesting to synthesize anthracycline analogues of **1a**,**b** in which the B or D-ring is heteroaromatic, since a heteroaromatic ring can provide a useful bioisosteric replacement of the benzene ring in some drugs.[8] As a part of our continuing studies on the practical synthesis of anthracyclines[2b,9] and their analogues,[10] we have briefly reported the first total synthesis of a D-ring indole analogue of **1a**.[11] We now report in detail the results of this investigation.

Recently we have reported an efficient, regiospecific synthesis of 4-demethoxydaunomycinone and daunomycinone by utilizing a strong base-induced cycloaddition of 4-acetoxy- and 4-methoxyhomophthalic anhydrides to 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone.[12] Therefore, we initially attempted to obtain the key *para*-acetoxylated cycloaddition product (**3**) by a similar method to that described for 4-demethoxydaunomycinone and daunomycinone. However, *para*-oxidation of the previously obtained tetracyclic compound (**2**)[13] with lead tetraacetate (LTA) did not give the *para*-acetoxylated compound (**3**) at all and an attempt to prepare 4-acetoxy-5-methylpyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-dione (**5**) by LTA-oxidation of the ketene silyl acetal intermediate generated from (3-carboxy-1-methylindol-2-yl)acetic acid (**4**) followed by dehydration also failed[14] (Chart 1). The LTA-oxidation method was unsatisfactory in the present case, probably owing to the instability of the indole nucleus.

The useful 2-methoxy-(3-carboxyindolyl)acetic acid (**8**) was obtained by the hypervalent iodine oxidation of methyl 3-methoxycarbonyl-1-methylindol-2-yl acetate



LDA = lithium diisopropylamine

Chart 1

(**6**). Treatment of **6** with $PhI(OAc)_2$ (phenyliodosyl diacetate, PIDA) in methanolic sodium methoxide gave the 2′-methoxy ester (**7**) in 37% yield.[15] Saponification of **7** with ethanolic KOH under reflux followed by dehydration with (trimethylsilyl)ethoxyacetylene[16] in dichloroethane gave the 4-methoxy-5-methylpyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-dione (**9**) in 87% overall yield. Conversion of the anhydride (**9**) to the pentacyclic adducts (**10**, **14**, and **15**) was carried out by our strong base-induced cycloaddition method.[2b,12,17] Treatment of the sodium salt generated from **9** and 1.1 eq of NaH in tetrahydrofuran (THF) with 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (**11**) at room temperature gave the regiospecific cycloadduct (**10**) in 57% yield. The cycloaddition of **9** was shown to proceed with the same regiochemistry[13] as that of the parent anhydride (**12**) in the reaction with 3-bromo-5-hydroxy-1,4-naphthoquinone (**13**) giving the single cycloadduct (**14**) [not the regioisomer (**14′**)].[18] The regioisomeric cycloadduct (**15**) was obtained by the reaction of the sodium salt of **9** with 2-chloro-7,7-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (**16**) in 55% yield (Chart 2).

The cycloadduct (**10**) was readily hydrolyzed quantitatively to give an 81% yield of the triketone (**17**) with aqueous trifluoroacetic acid (CF_3CO_2H). Side chain elaboration of the enolizable 9-keto group of **17** was accomplished by the use of (trimethylsilyl)ethynylcerium (III) chlo-

ride.[19] Treatment of **17** with 20 eq of (trimethylsilyl)ethynylcerium (III) chloride [prepared from (trimethylsilyl)ethynyllithium and cerium (III) chloride in THF] at $-78\,^{\circ}C$ gave a 9-trimethylsilylethynyl alcohol (**18**) in 71% yield. Direct conversion of the trimethylsilylethynyl group of **18** into the methyl ketone group was accomplished by the treatment with HgO/dilute H_2SO_4 in boiling THF to give the α-hydroxyketone compound (**19**) in 87% yield. Introduction of a C-11 *cis*-hydroxyl group into **19** was performed by bromination of its acetal derivative (**20**) and subsequent hydrolysis.[9,20] Acetalization of **19** with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in boiling benzene gave the acetal (**20**) in 82% yield. Bromination of **20** with bromine and 2,2′-azobisisobutyronitrile (AIBN) in a mixture of H_2O–CCl_4–$CHCl_3$ under reflux and subsequent hydrolysis with 80% aqueous CF_3CO_2H at 0 °C gave the *cis*-9,11-diol (**21**) in 22% yield. The *cis*-stereochemistry was deduced from the coupling constant [δ 5.25—5.35 (m, 1H, $v_{1/2}=8.0$ Hz, H-11 eq)][21] and the successful conversion into the *cis*-benzoboronate intermediate (**22**)[22]: reaction of the 9,11-diol (**21**) with benzeneboronic acid in CF_3CO_2H–anhydrous toluene at room temperature provided the cyclic *cis*-boronate (**22**), which was hydrolyzed with 2-methyl-2,4-pentanediol in AcOH to give the 9,11-diol in 82% yield. This was identical with the *cis*-9,11-diol (**21**).

The desired (9*S*,11*S*)-α-glycoside (**24**) was obtained by the condensation of the aglycone (**21**) with appropriately protected daunosamine (**23**) under the reaction conditions developed by Terashima *et al.*[23] Thus, **21** and suitably modified L-daunosamine (**23**) were treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and molecular sieves 4A in a mixed solvent of anhydrous CH_2Cl_2 and anhydrous ether at $-15\,^{\circ}C$ to give three α-glycosides. These glycosides were separated by preparative thin layer chromatography (TLC) on silica gel and deprotected with an equivalent amount of 0.1 N NaOH at 0 °C to give the natural-type (9*S*,11*S*)-α-glycoside (**24**) (24% yield based on **21**), the (9*R*,11*R*)-α-glycoside (**25**) (38% from **21**), and the (9*S*,11*S*)-α-glycoside (**26**) (14% from **21**). These absolute structures were adequately supported by the spectral data (circular dichroism (CD) and proton nuclear magnetic resonance (^{1}H-NMR), see Experimental section). The similarity of the CD curves of **24** and **26** to that of natural daunomycin (**1a**) ($[\theta]_{287}$ -1.72×10^4 (MeOH)) indicated that **24** and **26** had the natural configuration (9*S*, 11*S*), whereas the CD curve of **25** indicated the opposite configuration (9*R*, 11*R*), and the small $v_{1/2}$ value (6.0 Hz) of the ^{1}H-NMR signals due to their anomeric protons indicated that they were α-glycosides.[6b,24] The D-ring indole analogue (**24**) shows inhibitory activity against L-1210 cell growth (*in vitro*) comparable to that of adriamycin (**1b**).

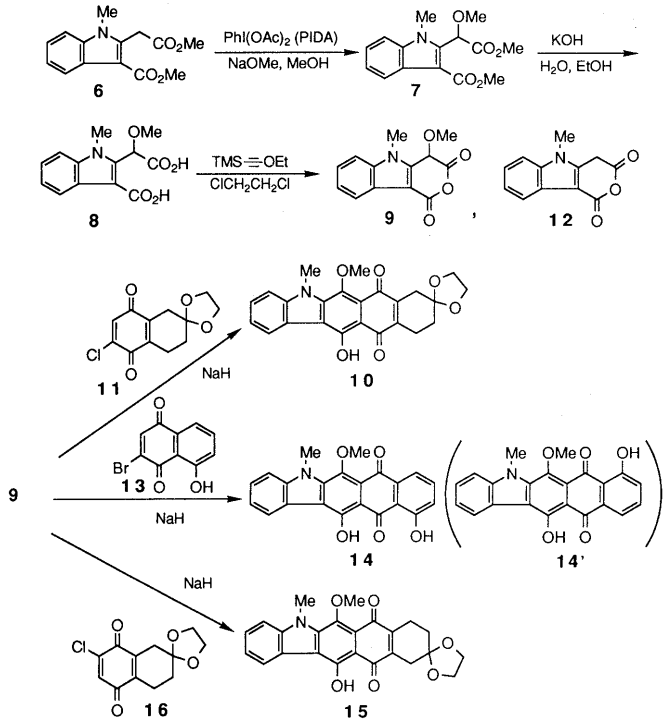


Chart 2

Experimental

All melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared (IR) absorption spectra were

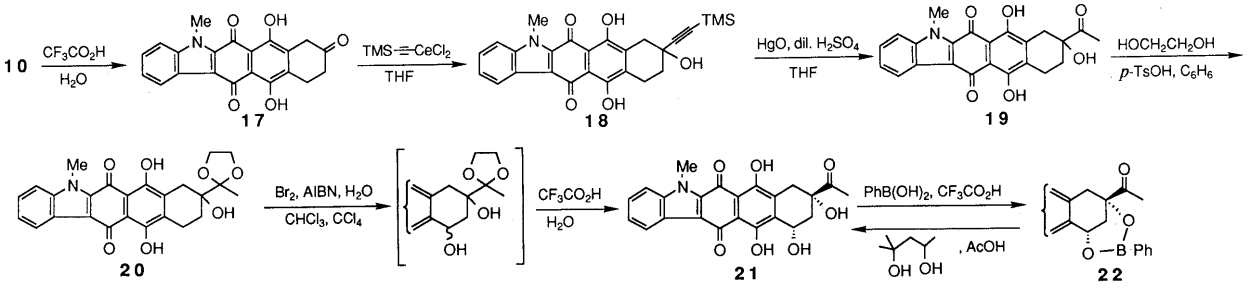


Chart 3

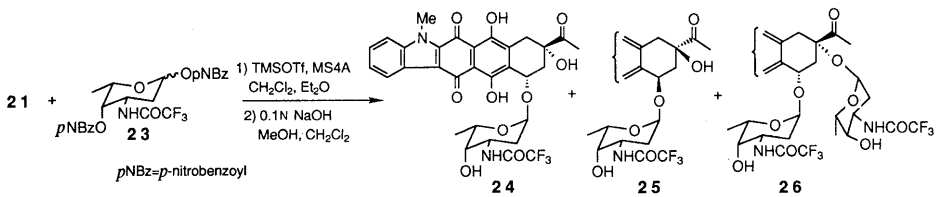


Chart 4

recorded on a JASCO HPIR-102 spectrophotometer. ^{1}H-NMR spectra were determined on a Hitachi R-22 (90 MHz), a JEOL JNM FX-90Q (90 MHz), or a JEOL JNM-GX500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained by the electron impact (EI) method unless otherwise noted, on an ESCO EMD-05A (for EI-MS), a JEOL JMS-D300 (for EI- and exact MS), or a JEOL HX-100 (for fast atom bombardment (FAB)-MS) mass spectrometer. CD spectra were obtained on a JASCO J-500A spectropolarimeter. E. Merck Silica gel 60 (0.063—0.200 mm, 70—230 mesh ASTM) and E. Merck pre-coated TLC plates, Silica gel 60 F_{254} were used for column chromatography and for preparative thin layer chromatography (preparative TLC), respectively.

Methyl 2-Methoxy-(3-methoxycarbonyl-1-methylindol-2-yl)acetate (7) Methyl 3-methoxycarbonyl-1-methylindol-2-yl acetate (**6**)[25] (1.0 g, 3.38 mmol) was added to a stirred solution of Na (308 mg, 13.4 mmol) in dry MeOH (40 ml) at room temperature under nitrogen. The mixture was stirred for a few minutes under the same conditions and $C_6H_5I(OAc)_2$ (1.41 g, 4.39 mmol) was added. The resulting slurry was stirred at room temperature for 3 d, poured into 10% HCl, made neutral, and extracted with CH_2Cl_2 (70 ml × 2). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : Et_2O = 1 : 1) to give a 37% yield (364 mg) of **7** as colorless crystals, mp 125—126 °C (MeOH). IR ($CHCl_3$) ν: 1745, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (s, 3H, CH_3), 3.98 (S, 3H, CH_3), 4.04 (s, 3H, CH_3), 4.19 (s, 3H, CH_3), 6.68 (s, 1H, CH), 7.7—7.2 (m, 3H, ArH), 8.2—8.4 (m, 1H, ArH). Exact MS Calcd for $C_{15}H_{19}NO_5$: 291.1107. Found: 291.1108.

2-Methoxy-(3-carboxy-1-methylindol-2-yl)acetic Acid (8) A solution of **7** (836 mg, 2.87 mmol) in 30% aqueous KOH (5 ml) and EtOH (20 ml) was heated under reflux for 1 h. The mixture was poured into water (15 ml), adjusted to pH 1 by addition of concentrated HCl, and extracted with AcOEt (30 ml × 4). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an 86% yield of **8** (690 mg) as colorless crystals, mp 196—202 °C (hexane–Et_2O). IR (KCl) ν: 3200—2100, 1705, 1650 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.45 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.49 (s, 1H, CH), 7.1—7.6 (m, 3H, ArH), 7.9—8.3 (m, 1H, ArH). MS *m/z*: 263 (M^+).

4-Methoxy-5-methylpyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-dione (9) A suspension of **8** (670 mg, 2.55 mmol) and 2-(trimethylsilyl)ethoxyacetylene (746 mg, 5.25 mmol) in $ClCH_2CH_2Cl$ (60 ml) was stirred at 50 °C for 2 d. The reaction mixture was concentrated *in vacuo* to give a quantitative yield (625 mg) of **9** as colorless crystals, mp 270—275 °C (THF). IR (KCl) ν: 1780, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.81 (s, 1H, CH), 7.0—8.1 (m, 4H, ArH). Exact MS Calcd for $C_{13}H_{11}NO_4$: 245.0685. Found: 245.0672.

9,9-Ethylenedioxy-13-hydroxy-6-methoxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-7,12-dione (10) A mixture of **9** (53 mg, 0.216 mmol) and NaH (60% in mineral oil 9.6 mg, 0.24 mmol) in dry THF (5 ml) was stirred at room temperature for 20 min under a nitrogen atmosphere, then a solution of **11** (56 mg, 0.22 mmol) in dry THF (5 ml) was added. The reaction mixture was stirred at room temperature for 4 h, then quenched with saturated aqueous NH_4Cl (20 ml), and extracted with CH_2Cl_2 (20 ml × 3). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give a 57% yield (52 mg) of **10** as red crystals, mp 269—277 °C ($CHCl_3$–Et_2O). IR ($CHCl_3$) ν: 1640, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (m, 2H, H-10 × 2), 2.6—2.9 (m, 4H, H-8 × 2 and H-11 × 2), 3.98 (s, 3H, NMe), 4.05 (s, 4H, OCH_2CH_2O), 4.22 (s, 3H, OMe), 7.2—7:5 (m, 3H, ArH), 8.3—8.5 (m, 1H, ArH), 14.28 (s, 1H, ArOH). Exact MS Calcd for $C_{24}H_{21}NO_6$: 419.1366. Found: 419.1356.

11,13-Dihydroxy-6-methoxy-5-methyl-5*H*-naphtho[2,3-*b*]carbazole-7,12-dione (14) A solution of 2-bromo-8-hydroxy-1,4-naphthoquinone (**13**) (16.4 mg, 0.065 mmol) in dry THF (5 ml) was added to a stirred suspension of **9** (37 mg, 0.15 mmol) and NaH (60% in mineral oil, 7 mg, 0.175 mmol) in dry THF (10 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 14 h under the same conditions, then quenched with saturated aqueous NH_4Cl (15 ml). The aqueous layer was adjusted to pH 2 by addition of 1 N HCl and extracted with CH_2Cl_2 (20 ml × 3). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (hexane : Et_2O = 2 : 1) to give a 62% yield (15.1 mg) of **14**, mp 278—282 °C (C_6H_6). IR ($CHCl_3$) ν: 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (s, 3H, CH_3), 4.28 (s, 3H, CH_3), 7.36 (m, 1H, ArH), 7.42 (t, 1H, J = 7.0 Hz, ArH), 7.52 (d, 1H, J = 8.0 Hz, ArH), 7.60 (t, 1H, J = 7.0 Hz, ArH), 7.64 (t, 1H, J = 8.0 Hz, ArH), 7.84 (d, 1H, J = 6.5 Hz, ArH), 8.50 (d, 1H, J = 8.0 Hz, ArH), 12.41 (s, 1H, ArOH), 14.01 (s, 1H, ArOH). Exact MS calcd for $C_{22}H_{15}NO_5$: 373.0948. Found: 373.0925.

10,10-Ethylenedioxy-13-hydroxy-6-methoxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-7,12-dione (15) By the same procedure as described for the preparation of **10**, a 56% yield of **15** (24 mg) was obtained from **9** (25 mg, 0.10 mmol), NaH (60% in mineral oil 4.8 mg, 0.12 mmol), and **16** (26 mg, 0.10 mmol). Recrystallization from CH_2Cl_2–Et_2O gave a pure sample as red crystals. mp 168 °C (dec.). IR (KCl) ν: 1640, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.1 (m, 2H, H-9 × 2), 2.7—2.9 (m, 4H, H-8 × 2 and H-11 × 2), 3.97 (s, 3H, NMe), 4.06 (s, 4H, OCH_2CH_2O), 4.21 (s, 3H, OMe), 7.2—7.5 (m, 3H, ArH), 8.3—8.5 (m, 1H, ArH), 14.20 (s, 1H, ArOH). Exact MS Calcd for $C_{24}H_{21}NO_6$: 419.1366. Found: 419.1358.

7,12-Dihydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]-carbazole-6,9,13-trione (17) A solution of **10** (20 mg, 0.048 mmol) in CF_3CO_2H (4 ml) and water (1 ml) was heated at 50 °C for 2 h, then concentrated *in vacuo*, and the residue was partitioned between $CHCl_3$ (30 ml) and water. The aqueous layer was extracted with $CHCl_3$ (30 ml × 2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel ($CHCl_3$) to give an 81% yield (14 mg) of **17**, mp 269—277 °C ($CHCl_3$–Et_2O). IR (KCl) ν: 1710, 1600 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.65 (t, 2H, J = 7.5 Hz, H-10 × 2), 3.24 (t, 2H, J = 7.5 Hz, H-11 × 2), 3.62 (s, 2H, H-8 × 2), 4.30 (s, 3H, NMe), 7.30—7.55 (m, 3H, ArH), 8.44 (d, 1H, J = 8.0 Hz, ArH), 13.25 (s, 1H, ArOH), 13.89 (s, 1H, ArOH). Exact MS Calcd for $C_{21}H_{15}NO_5$: 361.0951. Found: 361.0968.

(±)-7,9,12-Trihydroxy-5-methyl-9-(trimethylsilyl)ethynyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (18) Anhydrous $CeCl_3$ (1.6 g, 6.7 mmol) was heated *in vacuo* (0.1 mmHg) at 140 °C for 2 h, and cooled under a nitrogen atmosphere, then dry THF (10 ml) was added. The resulting suspension was stirred at room temperature for 1 h and cooled to −78 °C. Lithium trimethylsilylacetylide [prepared from trimethylsilylacetylene (0.95 ml, 6.68 mmol) and *n*-BuLi (1.6 N, 2.8 ml, 4.48 mmol) in dry THF (10 ml) at −40 °C for 30 min] was added to the cooled suspension with stirring. The mixture was stirred at −78 °C for 1 h and then used as a dry THF solution of trimethylsilylethynylcerium (III) chloride. To this solution was added a solution of **17** (50 mg, 0.14 mmol) in dry THF (60 ml) at −78 °C under nitrogen. The mixture was stirred for 2 h under the same conditions, then quenched with water (50 ml), made acidic with 1 N HCl, and extracted with CH_2Cl_2 (120 ml × 3). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (hexane : AcOEt = 5 : 1) gave a 71% yield (44 mg) of **18** as red crystals, mp 111—114 °C (C_6H_6–hexane). IR (KCl) ν: 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.18 (s, 9H, $SiMe_3$), 2.0—2.2 (m, 2H, H-10 × 2), 2.8—3.0 (m, 4H, H-8 × 2 and H-11 × 2), 4.03 (s, 3H, NMe), 7.25—7.3 (m, 3H, ArH), 8.1—8.5 (m, 1H, ArH), 13.13 (s, 1H, ArOH), 13.66 (s, 1H, ArOH). Exact MS Calcd for $C_{26}H_{25}NO_5Si$: 459.1499. Found: 459.1492.

(±)-9-Acetyl-7,9,12-trihydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (19) A solution of **18** (21 mg, 0.046 mmol), HgO (25 mg, 0.116 mmol), and 3 M H_2SO_4 (0.6 ml) in THF (10 ml) was heated under reflux for 1.5 h and then cooled to room temperature. The reaction mixture was diluted with 5% HCl (15 ml) and extracted with CH_2Cl_2 (30 ml × 3). The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 10 : 1) to give an 87% yield (16.5 mg) of **19** as red crystals, mp 291—294 °C (CH_2Cl_2–AcOEt). IR (KCl) ν: 1685, 1605 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.8—1.9 (m, 2H, H-10 × 2), 1.9—2.0 (m, 2H, H-11 × 2), 2.32 (s, 3H, $COCH_3$), 2.84 (d, 1H, J = 18.0 Hz, H-8), 2.96 (d, 1H, J = 18.0 Hz, H-8), 4.22 (s, 3H, NMe), 7.3—7.5 (m, 3H, ArH), 8.45 (d, 1H, ArH), 13.40 (s, 1H, ArOH), 13.90 (s, 1H, ArOH). Exact MS Calcd for $C_{23}H_{19}NO_6$: 405.1213. Found: 405.1229.

(±)-9-[1,1-(Ethylenedioxy)ethyl]-7,9,12-trihydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (20) A mixture of **19** (25 mg, 0.061 mmol), ethylene glycol (0.04 ml, 0.70 mmol) and *p*-toluenesulfonic acid (2 mg) in C_6H_6 (7 ml) was refluxed for 3 h with azeotropic removal of water formed using a Dean–Stark apparatus. After being cooled, the mixture was partitioned between CH_2Cl_2 (35 ml) and saturated aqueous $NaHCO_3$ (10 ml), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 ml × 2), and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give an 82% yield (22.8 mg) of **20** as red crystals, mp 255—257 °C ($CHCl_3$–CCl_4). IR (KCl) ν: 1600 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 1.43 (s, 3H, H-15×3), 1.9—2.2 (m, 2H, H-10×2), 2.7—3.1 (m, 4H, H-8×2 and H-11×2), 4.05 (s, 4H, OCH_2CH_2O), 4.19 (s, 3H, NMe), 7.2—7.5 (m, 3H, ArH), 8.1—8.5 (m, 1H, ArH), 13.27 (s, 1H, ArOH), 13.78 (s, 1H, ArOH). Exact MS Calcd for $C_{25}H_{23}NO_7$: 449.1475. Found: 449.1498.

(9*RS*,11*RS*)-9-Acetyl-7,9,11,12-tetrahydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (21) A solution of bromine (100 mg, 0.625 mmol) in CCl_4 (4 ml) was added to the two-phase solution of **20** (50 mg, 0.111 mmol) and AIBN (60 mg, 6.36 mmol) in a mixture of $CHCl_3$ (60 ml), CCl_4 (8 ml), and H_2O (10 ml). The reaction mixture was heated under reflux for 12 h. After being cooled, the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (15 ml), and the organic layer was separated. The aqueous layer was extracted with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel ($CHCl_3$: MeOH = 10 : 1) to give a crude product, which was dissolved in aqueous 80% CF_3CO_2H (15 ml) and stirred at 0 °C for 1.5 h. The reaction mixture was poured into ice-water and extracted with $CHCl_3$ (30 ml×3). The extracts were combined and washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$: Et_2O = 5 : 1) to give **22** as red crystals (10.3 mg, 22% yield from **20**), mp 110—116 °C (hexane–C_6H_6). IR (KCl) ν: 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.1—2.3 (m, 2H, H-10×2), 2.43 (s, 3H, $COCH_3$), 2.95 (m, 1H, H-8), 3.07 (m, 1H, H-8), 4.24 (s, 3H, NMe), 5.25—5.35 (m, 1H, $\nu_{1/2}$ = 8.0 Hz, H-11), 7.40—7.45 (m, 3H, ArH), 8.1—8.4 (m, 1H, ArH), 13.12 (s, 1H, ArOH), 13.98 (s, 1H, ArOH). Exact MS Calcd for $C_{23}H_{19}NO_7$: 421.1159. Found: 421.1149.

(±)-9-Acetyl-7,12-dihydroxy-5-methyl-6,13-dioxo-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-9,11-diyl Phenylboronate (22) Under a nitrogen atmosphere, a mixture of **21** (12 mg, 0.029 mmol), benzeneboronic acid (9 mg, 0.074 mmol), CF_3CO_2H (0.05 ml) and dry toluene (2 ml) was stirred at room temperature for 14.5 h. The reaction mixture was quenched with 5% aqueous $NaHCO_3$ (3 ml) and extracted with benzene (10 ml×2). The extract was washed twice with water, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **22** (14.7 mg). Recrystallization from hexane–C_6H_6 gave a pure sample as red crystals: mp 232—235 °C. IR (KCl) ν: 1715, 1640, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.4 (m, 2H, H-10×2), 2.57 (s, 3H, $COCH_3$), 3.15—3.25 (m, 2H, H-8×2), 4.20 (s, 3H, NMe), 5.75—5.80 (m, 1H, H-11), 7.2—7.6 (m, 5H, ArH), 7.6—8.0 (m, 3H, ArH), 8.2—8.3 (m, 1H, ArH), 13.02 (s, 1H, ArOH), 13.85 (s, 1H, ArOH). MS *m/z*: 507 (M^+).

(9*RS*,11*RS*)-9-Acetyl-7,9,11,12-tetrahydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (21) Crude **22** (7 mg, 0.014 mmol) was stirred in a mixture of 2-methyl-2,4-pentanediol (0.1 ml), AcOH (0.1 ml), CH_2Cl_2 (1 ml) and acetone (1 ml) at room temperature for 3 h. The reaction mixture was poured into a mixture of CH_2Cl_2 (10 ml) and saturated aqueous $NaHCO_3$ (3 ml). The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was washed with *n*-pentane (10 ml×2) and purified by column chromatography on silica gel ($CHCl_3$: Et_2O = 5 : 1) to give an 82% yield (4.7 mg) of **21**, which was identical with an authentic sample obtained from **20**.

(+)-(9*S*,11*S*)-11-*O*-(3′-*N*-Trifluoroacetyl-α-L-daunosaminyl)-9-acetyl-7,9,12-trihydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (24), Its (−)-(9*R*,11*R*)Diastereomer (25), and (−)-(9*S*,11*S*)-9,11-*O*-Bis(3′-*N*-trifluoroacetyl-α-L-daunosaminyl)-9-acetyl-7,12-dihydroxy-5-methyl-8,9,10,11-tetrahydro-5*H*-naphtho[2,3-*b*]carbazole-6,13-dione (26) Under a nitrogen atmosphere, TMSOTf (0.014 ml, 0.074 mmol) was added to a stirred suspension of molecular sieves 4A (0.4 mg) and **23** (19 mg, 0.035 mmol) in dry CH_2Cl_2 (6 ml) and dry Et_2O (2 ml) at −40 °C. The mixture was stirred at −5 °C for 1 h and then cooled to −15 °C, and a solution of (±) **21** (11.5 mg, 0.027 mmol) in dry CH_2Cl_2 (5 ml) was added to it. After being stirred for 4 h under the same conditions, the mixture was poured into a vigorously stirred mixture of AcOEt (18 ml) and saturated aqueous $NaHCO_3$ (16 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt (8 ml). The combined organic layer was washed twice with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Separation of the residue by preparative TLC (CH_2Cl_2 : AcOEt = 20 : 1) gave three crude products. Each of them was dissolved in a solution of CH_2Cl_2 (0.5 ml) and MeOH (5 ml) under a nitrogen atmosphere, and 0.1 N NaOH (0.09 ml) was added to each solution at 0 °C. The mixture was stirred for 30 min under the same conditions, then one drop of AcOH was added. The resulting mixture was partitioned between AcOEt (10 ml) and brine (5 ml) and the separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2 : acetone = 10 : 1) gave a 24% yield (4.2 mg) of **24**, a 38% yield (6.7 mg) of **25**, and a 14% yield (3.3 mg) of **26**, each as red crystals. **24**: mp 114—118 °C (CCl_4–$CHCl_3$). $[\alpha]_D^{25}$ +37° (*c* = 0.15, $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1710, 1600 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.32 (d, 3H, *J* = 6.5 Hz, H-6′×3), 1.85 (td, 1H, *J* = 13.0, 4.5 Hz, H-2′), 2.02 (dd, 1H, *J* = 13.0, 4.5 Hz, H-2′), 2.15 (dd, *J* = 15.0, 2.0 Hz, H-10), 2.32 (br d, *J* = 15 Hz, H-10), 2.43 (s, 3H, $COCH_3$), 2.96 (d, 1H, *J* = 18.5 Hz, H-8), 3.26 (dd, 1H, *J* = 18.5, 2.0 Hz, H-8), 3.68—3.76 (m, 1H, 4′-H), 4.19—4.29 (m, 2H, H-3′ and H-5′), 4.30 (s, 3H, NMe), 4.33 (s, 1H, OH-9), 5.27 (br d, 1H, *J* = 2.0 Hz, $\nu_{1/2}$ = 6.0 Hz, H-11), 5.55 (d, 1H, *J* = 4.5 Hz, $\nu_{1/2}$ = 6.0 Hz, H-1′), 6.65 (d, 1H, *J* = 8.0 Hz, NH), 7.51—7.55 (m, 3H, ArH), 8.42 (d, *J* = 8.0 Hz, ArH), 13.24 (s, 1H, ArOH), 14.03 (s, 1H, ArOH). FAB-MS (negative) *m/z*: 645 [$(M-H)^-$]. CD (EtOH) $[\theta]_{max}$ (nm): -1.4×10^3 (320). **25**: mp 101—105 °C (CCl_4–$CHCl_3$). $[\alpha]_D^{25}$ −273° (*c* = 0.15, $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1710, 1600 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.32 (d, 3H, *J* = 6.5 Hz, H-6′×3), 1.86—2.50 (m, 4H, H-2′×2 and H-10×2), 2.42 (s, 3H, $COCH_3$), 3.01 (d, 1H, *J* = 19.0 Hz, H-8), 3.29 (dd, *J* = 19.0, 1.5 Hz, H-8), 3.60—3.68 (m, 1H, H-4′), 4.30—4.40 (m, 1H, H-3′), 4.32 (s, 3H, NMe), 4.51 (s, 1H, OH-9), 4.57 (q, 1H, *J* = 6.5 Hz, H-5′), 5.36 (d, 1H, *J* = 4.0 Hz, $\nu_{1/2}$ = 6.0 Hz, H-1′), 5.54 (t, 1H, *J* = 2.0 Hz, $\nu_{1/2}$ = 6.0 Hz, H-11), 6.69 (d, 1H, *J* = 8.0 Hz, NH), 7.50—7.60 (m, 3H, ArH), 8.42 (d, 1H, ArH), 13.26 (s, 1H, ArOH), 14.18 (s, 1H, ArOH). FAB-MS (negative) *m/z*: 645 [$(M-H)^-$]. CD (EtOH) $[\theta]_{max}$ (nm): $+5.0\times10^3$ (320). **26**: mp 255—260 °C (CCl_4–$CHCl_3$). $[\alpha]_D^{25}$ −46° (*c* = 0.05, $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1600 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.55 (d, 3H, *J* = 6.5 Hz, H-6″×3), 1.38 (d, 3H, *J* = 7.0 Hz, H-6′×3), 1.81—2.04 (m, 5H, H-2′×2, H-2″×2 and H-10), 2.33 (s, 3H, $COCH_3$), 2.54 (d, 1H, *J* = 13.0 Hz, H-10), 2.95 (d, 1H, *J* = 19.0 Hz, H-8), 3.65 (dd, 1H, *J* = 19.0, 2.0 Hz, H-8), 3.78 (br s, 1H, H-3″), 3.90—3.93 (m, 2H, H-4′ and H-4″), 4.26—4.28 (m, 1H, H-3′), 4.29 (s, 3H, NMe), 4.38—4.42 (m, 1H, H-5′), 4.57 (q, *J* = 6.5 Hz, H-5″), 4.95 (m, 2H, $\nu_{1/2}$ = 6.0 Hz, H-11 and H-1″), 5.47 (m, 1H, $\nu_{1/2}$ = 6.0 Hz, H-1′), 6.75 (d, 1H, *J* = 8.5 Hz, NH), 6.83 (d, 1H, *J* = 8.0 Hz, NH), 7.39—7.53 (m, 3H, ArH), 8.41 (d, 1H, *J* = 8.0 Hz, ArH), 13.36 (s, 1H, ArOH), 14.02 (s, 1H, ArOH). FAB-MS (negative) *m/z*: 870 [$(M-H)^-$]. CD (EtOH) $[\theta]_{max}$ (nm): -5.1×10^3 (320).

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