Synthesis of 11-Deoxydaunomycinone and Novel 10-Fluoroanthracyclinone Derivatives

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11-Deoxydaunomycinone **15** and 10-fluoroanthracyclinone derivatives **9**, **10** were obtained. Naphthalenone **4** prepared from 2-(2,4-pentadienyl)-1,3-dioxane **2** with methyl vinyl ketone and hydrolysis with $HClO_4$ was condensed with phthalidesulfone **5** through Michael type reaction, and was converted to **7** by epoxidation. Epoxide **7** was transformed to trione **12** using reduction-oxidation or hydrofluorination process, and then to **15** by introducing several functional groups. Compound **8** obtained in the course of the reaction of epoxide **7** and HF/Pyr was used for the synthesis of compounds **9**, **10**.

Introduction

The anthracycline anticancer antibiotics adriamycin (doxorubicin) (**1a**), daunorubicin (daunomycin) (**1b**), carminomycin (**1c**), and idarubicin (**1d**) have been proved to be effective chemotherapeutics against several types of human cancer.[1] The total synthesis of these glycosides and related derivatives have been the objects of many synthetic studies. Numerous elegant and ingenious strategies[2] have been devised to produce isomerically pure intermediates as precursors for daunomycinone and its 11-deoxyderivatives since the original synthesis of these compounds by Wong.[3] The synthesis of various 11-deoxyanthracycline derivatives using these synthetic strategies have been also reported.[4] 11-Deoxydaunorubicin (**1e**) isolated from *micromonospora peucetica n. sp.* by Arcamone[5] in 1980 has been known to have less cardiotoxicity than the previously reported anthracyclines. Similar results have been obtained by Tone[6] in 1985 that the cardiotoxicity was surprisingly diminished when the hydroxyl group of aclacinomycin derivatives was substituted by an hydrogen atom at C-11 position.

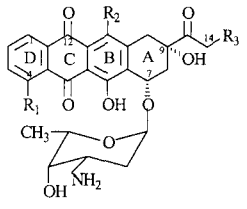
In this paper, we describe the synthesis of 11-deoxydaunorubicinone **15** through ring annelation from phthalide sulfone and transformation of functional groups. In the course of the work, we report also the synthesis of 10-fluroanthracyclinone derivative **9**, **10** using HF/pyridine.

Results and Discussion

The synthesis of naphthalenone **4** to be used as a Michael acceptor was applied by the synthetic method of 6-ethylnaphthalenone which was previously reported.[7] Diene **2** was prepared from acrolein and phosphonium salt, obtained from 2-(2-bromoethyl)-1,3-dioxane and triphenylphosphine. Diels-Alder reaction of this diene **2** and methyl vinyl ketone afforded adduct **3** in 94% yield. Adduct **3** was transformed to mixed naphthalenone **4** as *cis/trans* (5 : 2) form by hydrolysis in 3N aqueous $HClO_4$. Because the bridging B-ring is apt to be converted to aromatic ring when the isomer is condensed with phthalide sulfone **5**, the mixed product was directly used in the next step without separation.

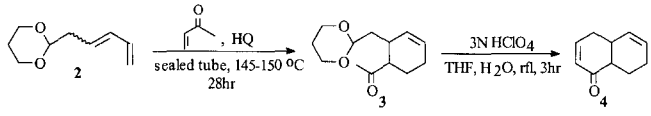
After preparation of diol (91%) by *in situ* internal Claisen condensation of phthalide sulfone **5** with naphthalenone **4** in *t*-BuOLi, a stable compound **6** was obtained in 85% through oxygen bubbling in DMF for 6hr.[8]

The double bond of compound **6** was utilized to introduce acetyl group at C-9 position for construction of daunomycinone structure. Epoxide **7** prepared from compound **6** with *m*-CPBA[9] was reduced by catalytic hydrogenation (H_2, Pd/C) to introduce a hydroxyl group at C-9 position.[10] The resulting compound **11** was transformed to trione **12** by oxidation with PCC.[11] According to our previous paper,[12] C-9 position of the epoxide compound having ethyl group is mainly attacked by F^- when the epoxide is treated with HF/Pyr (7 : 3) in $CHCl_3$. In contrast, C-9 and C-10 positions of the compound are equally attacked by F^- when the compound is treated with HF/Pyr (44 : 56) in $CHCl_3$.[12,7b] Therefore, we expected that C-9 position of epoxide **7** would be attacked by F^- if we used HF/Pyr (7 : 3) in $CHCl_3$. However, after the completion of the reaction within 5 min, only compound **8** attacked at C-10 position was obtained in good yield. It appears that F^- attacks more hindered position in

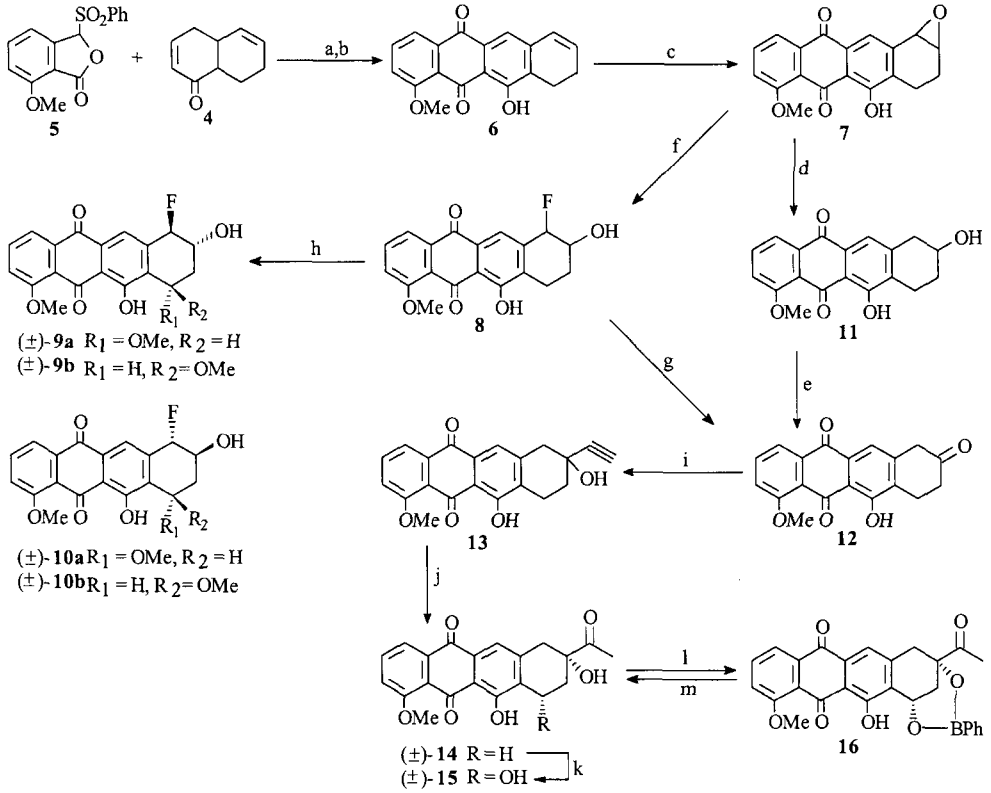


1a. Adriamycin R_1=OMe, R_2=R_3=OH
1b. Daunorubicin R_1=OMe, R_2=OH, R_3=H
1c. Carminomycin R_1=R_2=OH, R_3=H
1d. Idarubicin R_1=R_3=H, R_2=OH
1e. 11-Deoxydaunorubicin R_1=OMe, R_2=R_3=H

Figure 1



Scheme 1



Scheme 2. (a) *t*-BuOLi/THF, -78 °C, rt (b) oxygen/DMF, rfl, 6hr (c) mCPBA/MC, 0 °C (d) H_2, 10% Pd/C, triethanolamine/EtOH, 31 psi, 3.5 h (e) PCC/CH_2Cl_2, rt (f) HF/Pyr (7 : 3)/$CHCl_3$, 0 °C, 5 min (g) HF/Pyr (7 : 3)/$CHCl_3$, 0 °C, rt 10 h (h) PVPHP, AIBN/CCl_4, FCC (MeOH) (i) $CeCl_3$, (trimethylsilyl)ethynyllithium/THF, -78 °C (j) HgO, 20% H_2SO_4/THF, rfl (k) NBS, AIBN/CCl_4, rfl, CF_3COOH (l) $PhB(OH)_2$, *p*-TsOH/toluene (m) 2-methyl-2,4-pentanediol, AcOH/CH_2Cl_2/acetone.

acidic condition and F^- attacks less hindered position in basic condition.[13] Compound **8** was obtained in isomeric mixture of F_{eq}-OH_{eq}/F_{ax}-OH_{ax} (8 : 1) determined from ^1H NMR data. Their configurations were easily determined by analyzing scalar coupling constants in NMR spectra of compounds **9a** and **10a** of the next step. For the F_{eq}-OH_{eq} conformation, $^3J_{10\text{-}H,9\text{-}H}$ = 7.8 Hz, $^3J_{10\text{-}F,8\text{-}C}$ = 6.0 Hz, and $^4J_{10\text{-}F,8\text{-}H}$ = 5.6 Hz, and for the F_{ax}-OH_{ax} conformation, $^3J_{10\text{-}H,9\text{-}H}$ = 2.9 Hz, $^3J_{10\text{-}F,8\text{-}C}$ = ~ 0 Hz, and $^4J_{10\text{-}F,8\text{-}H}$ = ~ 0 Hz.

Using the same method, compound **12** was obtained in one step by treating epoxide **7** with HF/Pyr (7 : 3) in $CHCl_3$ at 0 °C and leaving it at room temperature for 8 h. The physical and spectral properties of this compound were identical in all respects with the product **12** obtained from alcohol **11**.

Now, to obtain compound **15** having anthracycline structure, acetyl group was introduced at C-9 position of compound **12**, and hydroxyl groups at C-7 and C-9 positions. First, after the reaction of trione **12** and (trimethylsilyl)ethynylcerium chloride (III) generated from (trimethylsilyl)ethynyl lithium and $CeCl_3$ to furnish ethynyl compound **13.** Compound **14** having acetyl and hydroxyl groups at C-9 was obtained by treating **13** with acid.[14] Selective hydroxylation at C-7 position can be achieved by converting carbonyl group at C-13 to acetal form and preventing the introduction of OH group to C-14 and C-10 positions.[15] But, in this study, we tried, though the yield was low, to introduce hydroxyl group directly to C-7 position without formation of acetal form. After bromination of **14** with Br_2 under AIBN as a catalyst in CCl_4, *cis* form of **15** as a major product was obtained by hydrolysis in 37% yield.[16] In contrast, the *trans*/*cis* (7 : 1, 40%) isomer of **15** was obtained when the treatment of trifluoroacetic acid was omitted in the hydrolysis. After binding of diol **15** obtained through the two methods with phenylboronic acid respectively, cleavage with 2-methyl-2,4-pentanediol produced *cis*-diol compound **15**.[17] The reaction of *cis*-diol **15** obtained from the latter reaction without using TFAA produced a trace amount on TLC. Therefore, it was confirmed again that the product of the former reaction was mostly *cis* form. The NMR spectrum of **15** exhibited different scalar coupling patterns; $^3J_{7\text{-}Heq,8\text{-}Hax}$ = 4.9 Hz, $^3J_{7\text{-}Heq,8\text{-}Hax}$ = 2.0 Hz for *cis* form and $^3J_{7\text{-}Hax,8\text{-}Hax}$ = 9.0, $^3J_{7\text{-}Hax,8\text{-}Heq}$ = 6.5 Hz for *trans* form.

Finally, without separation of the obtained isomeric mixture **8**, bromination with pyridinium hydrobromide perbromide (PVPHP) and AIBN in CCl_4 followed by FCC (flash column chromatography)[18] with methanol afforded **9a, b** and **10a, b** where methoxy group was introduced at C-7. The two F_{eq}-OH_{eq} and F_{ax}-OH_{ax} compounds in **8** gave major compounds **10a** and **9a** respectively where 7-OMe was introduced as an axial form for both compounds. However, we could not separate **9b** and **10b** because they were produced in trace amounts on TLC. From NMR spectrum analysis, it was confirmed that the methoxy group had been introduced as an axial form for both **9a** and **10a**; their 7-H

NMR peaks were both triplets having the scalar coupling $^3J_{7\text{-Heq},8\text{-Heq}} = 2.9$ Hz.

In summary, we synthesized the title compounds, 11-deoxydaunomycinone **15** and novel 10-fluroanthracyclinone derivative **9** and **10**, which were the aglycone for the synthesis of the glycoside.

Experimental Section

All reactions were carried out under nitrogen atmosphere with oven-dried glassware. All solvents were purified by distillation and dried, if necessary, prior to use. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DMX600, Bruker DRX300 and JEOL JNM EX-400 spectrometers. Chemical shifts were internally referenced to TMS for ^{1}H or to solvent signals for ^{13}C, or externally to CF_2Br_2 in $CDCl_3$ (δ = 7.0) for ^{19}F. Mass spectra were obtained on a JEOL JMX-DX 300 spectrometer (EI and FAB$^+$) and on a VG QUATTRO spectrometer (ESI). Melting points were obtained on a Büchi 510 melting point apparatus and were uncorrected. Products were purified by flash column chromatography on silica gel (60-200 mesh).

2-(2,4-Pentadienyl)-1,3-dioxane (2). The 2-(2-bromoethyl)-1,3-dioxane (10.0 g, 50.0 mmol) and triphenylphosphine (12.0 g, 46.0 mmol) in toluene (100 mL) were heated at reflux under dry nitrogen for 36 hrs. The cooled product was separated by filtration, washed well with dry ether, and dried under vacuum to afford [2-(1,3-dioxan-2-yl)ethyl] triphenylphosphonium bromide (16.7 g, 80%). The salt (22.0 g, 48 mmol) was suspended in 150 mL of tetrahydrofuran under dry nitrogen and treated with a solution of *n*-buthyllithium in hexane (1.3 molar equiv., 34.4 mL of a 1.4 M solution) at -20 °C. After 15 min, the nearly clear, red solution was cooled to -78 °C, and acrolein (2.1 g, 37.1 mmol) was added, discoloring the solution. The solution was then warmed to room temperature. The solvent was evaporated, and the oil was dissolved in methylene chloride. This solution was rinsed with 5% aqueous sodium sulfate solution and concentrated to the mixed dienes **7a** (4.5 g, 78%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.79 (4H, t), 3.88 (4H, t), 3.40 (4H, t), 1.90-1.71 (8H, m), and 1.55-1.43 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.11 (C), 115.36 (CH), 68.32 (OCH_2), 33.80 (CH_2), 32.66 (CH_2), 29.17 (CH_2), 27.90 (CH_2), and 25.27 (CH_2); IR (NaCl) cm^{-1} 2937, 2862, 1510, 1476, 1461, 1245, 1236, 1113, 1028, 824, 771, and 729 ; MS m/z: 154 (M$^+$)

1-Acety-2-[(1,3-dioxa-2-cyclohexyl)methyl]cyclohex-3-ene (3). Diene **2** (7.0 g, 45.4 mmol), methyl vinyl ketone (5.4 mL, 68.1 mmol), and hydroquinone (70 mg) were heated in a sealed tube at 145-150 °C for 28 h. The sealed tube was chilled to -78 °C and then opened, and the mixture was transferred to a flask. Excess methyl vinyl ketone was evaporated, and the residual oil was distilled *in vacuo* to give adduct **3** (9.6 g, 94%) as colorless liquid. A distilled material was used in the next reaction without separation into individual isomers. MS m/z : 224 (M$^+$)

4a,7,8,8a-Tetrahydro-1(4*H*)-naphthalenone (4). 3 N $HClO_4$ (40 mL) was added to a solution of **3** (6.0 g, 26.8 mmol) in THF (80 mL) and H_2O (40 mL). The reaction mixture was heated at reflux for 3 h. The THF was removed under vacuo, and the aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed successively with saturated $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered, and evaporated. The residue was distilled to give **4** (3.2 g, 81%) as colorless liquid. GC/MS analysis showed that this product was a mixture of *cis/trans* (5 : 2) isomers. A small amount of the distilled material was separated into individual isomers by prep-HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) *trans*: δ 6.96 (qd, J = 10.2, 2.5 Hz, 1H), 6.03 (dt, J = 10.2, 3.0 Hz, 1H), 5.82-5.44 (m, 2H), 2.64-1.80 (m, 6H), 1.64-1.30 (m, 2H). *cis*: δ 6.84 (dt, J = 10.2, 3.5 Hz, 1H), 5.96 (dt, J = 10.2, 1.6 Hz, 1H), 5.69-5.58 (m, 2H), 2.74-2.00 (m, 6H), 1.94-1.56 (m, 2H).

6-Hydroxy-4-methoxy-7,8-dihydronaphthacene-5,12-dione (6). Compound **6** was prepared from **4** and **5** according to our earlier procedure. To a cold (-78 °C) magnetically stirred solution of *t*-BuOLi, prepared from *t*-BuOH (4.0 mL, 42.5 mmol) and *n*-BuLi (35.4 mL of 1.2 M in THF, 42.5 mmol) in dry THF (40 mL) under N_2 was added the sulfone **5** (4.7 g, 15.6 mmol) as a slurry in THF (40 mL). Upon complete addition of the sulfone, the orange-yellow mixture of partially precipitated anion was stirred for 30 min at -78 °C. The solution of the naphthalenone **4** (2.1 g, 14.2 mmol) in THF (30 mL) was added by syringe, and the mixture was stirred at -78 °C for 2 h. The cooling bath was removed, and the reaction was allowed to warm to r.t., and then heat at reflux for 30 min. The mixture was cooled to 0 °C and acidified with 2N HCl. The THF was evaporated and the aqueous mixture was extracted with EtOAc. The combined EtOAc extracts were washed successively with H_2O and brine, dried, filtered and evaporated.

Oxygen was bubbled through a heated solution of the crude diol compound obtained above in DMF. The oxygen flow was terminated, and the solution was cooled to 0 °C. Addition of H_2O to the solution precipitated **7** as orange crystals, which were collected by filtration, washed with H_2O and dried. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/hexane, 6 : 1) to give **7** (3.9 g, 85%). mp 217-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.23 (s, 1H), 7.93 (dd, J = 7.5, 1.0 Hz, 1H), 7.69 (t, J = 8.4 Hz, 3H), 7.42 (s, 1H), 7.40 (d, J = 5.3 Hz, 1H), 6.51 (dt, J = 11.0, 1.0 Hz, 1H), 6.26 (dt, J = 11.0, 4.0 Hz, 1H), 4.05 (s, 3H), 2.92 (br.t, J = 8.0 Hz, 2H), 2.60-2.20 (m, 2H); MS m/z: 306 (M$^+$).

9,10-Epoxy-6-hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacenone-5,12-dione (7). To a cold (0 °C) solution of **7** (1.7 g, 5.6 mmol) in CH_2Cl_2 (150 mL) and buffer solution (80 mL, KH_2PO_4/Na_2HPO_4) was added 3-chloroperoxybenzoic acid (1.4 g, 6.7 mmol), and the mixture was stirred at 0 °C for 10 h. The organic layer was separated, washed successively with sat. aqueous $NaHCO_3$, 3% aqueous $NaHSO_3$ and brine, then filtered, and dried. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc, 95 : 5) to give **7** (1.7 g, 95%). mp 217-219 °C; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 13.24 (s,1H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.80 (s, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 7.0, 1.4 Hz, 1H), 4.05 (s, 3H), 3.94 (d, *J* = 11.1 Hz, 1H), 3.20 (dt, *J* = 11.1, 5.0 Hz, 1H), 2.45 (t, *J* = 5.0 Hz, 2H), 2.30-1.95 (m, 2H); MS m/z: 322 (M^+).

(±)-6,9-Dihydroxy-10-fluoro-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (8). Using polyethylene equipment and under strict exclusion of moisture, to a cooled (0 °C) solution of HF/Pyr (7 : 3, 42 mL) was added the epoxide **7** (1.2 g, 3.7 mmol) in $CHCl_3$ (50 mL) in one portion, and the mixture was stirred for 5 min under Ar at r.t. The reaction mixture was poured into ice water (50 mL) and extracted with CH_2Cl_2. The combined organic phases were evaporated to dryness, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 2 : 98 to CH_2Cl_2/EtOAc 10 : 90) to give **8** (83%, 1.1 g) as a dark yellow powder and **12** (15%, 0.2 g) as a light yellow powder. **8**: mp 220-223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.38 (s, 1H, 6-OH), 7.99 (dd, *J* = 7.8, 1.0 Hz, 1H, 1-H), 7.92 (s, 1H, 11-H), 7.76 (dd, *J* = 8.3, 7.8 Hz, 1H, 2-H), 7.37 (dd, *J* = 8.3, 1.0 Hz, 1H, 3-H), 5.41 (dd, *J* = 51.7, 7.8 Hz, 1H, 10-H), 4.21-4.11 (m, 1H, 9-H), 4.08 (s, 3H, 13-OMe), 3.11-3.04 (dt, *J* = 18.1, 4.6 Hz, 1H, 7-He), 2.87-2.78 (m, 1H, 7-Ha), 2.39 (d, *J* = 2.9 Hz, 1H, 9-OH), 2.30-2.22 (dm, *J* = 13.7 Hz, 1H, 8-He), 1.96-1.85 (m, 1H, 8-Ha); ^{13}C NMR ($CDCl_3$) δ 188.58 (C-5), 182.27 (C-12), 160.66 (C-4), 159.53 (C-6), 140.94 (d, $^2J_{F,C\text{-}10a}$ = 18.2 Hz, C-10a), 135.85 (C-2), 135.35 (C-12a), 133.33 (d, *J* = 3.6 Hz, C-6a), 130.19 (C-11a), 120.24 (C-4a), 119.83 (C-1), 118.17 (C-3), 117.54 (d, $^3J_{F,C\text{-}11}$ = 7.5 Hz, C-11), 114.97 (C-5a), 92.47 (d, $J_{F,C\text{-}10}$ = 176.8 Hz, C-10), 68.44 (d, $^2J_{F,C\text{-}9}$ = 19.5 Hz, C-9), 56.20 (OMe-13), 26.17 (d, $^3J_{F,C\text{-}8}$ = 6.1 Hz, C-8), 21.18 (C-7); IR (KBr pellet) 3396, 2920, 2850, 1738, 1670, 1628, 1579, 1516, 1462, 1381, 1280, 1231, 1178, 1068, 1023, 972, 892, 827, 860, 750, 680, 649 cm^{-1}; MS m/z: 342 (M^+)

(7S,9R,10R)-6,9-dihydroxy-4,7-dimethoxy-10-fluoro-5,12-naphthacenedione (9a), (7S,9S,10S)-6,9-dihydroxy-4,7-dimethoxy-10-fluoro-5,12-naphthacenedione (10a). Compound **8** (50.0 mg, 0.2 mmol) was dissolved in boiling CCl_4. Catalytic amount of AIBN and PVPHP (100.0 mg) were added. The solvent refluxed for 2 h. After cooling, the polymer was removed by filtration, the solution is concentrated and the residue chromatographed (FCC, elution with MeOH). The fractions containing **9a** and **10a** were evaporated and purified by column chromatography on silica gel to give **10a** (80%, 43.5 mg, R_f = 2.3, MC : EtOAc : Hexane = 2 : 1 : 0.5) as a yellow powder and **9a** (9%, 4.9 mg, R_f = 3.4, MC : EtOAc : Hexane = 2 : 1 : 0.5) as a orange solid. **10a**: mp 216-220 °C (dec.) **9a :** ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.52 (s, 1H, 6-OH), 7.98 (d, 1H, *J* = 7.8 Hz, 1-H), 7.94 (s, 1H, 11-H), 7.77 (dd, 1H, *J* = 7.8, 8.3 Hz, 2-H), 7.38 (d, 1H, *J* = 8.3 Hz, 3-H), 5.32 (dd, 1H, *J* = 51.8, 8.3 Hz, 10-H), 4.78 (t, 1H, *J* = 2.9 Hz, 7-H_e), 4.52-4.42 (m, 1H, 9-H), 4.08 (s, 3H, 13-OMe), 3.58 (s, 3H, 14-OMe), 2.53-2.44 (dm, 1H, *J* = 15.6 Hz, 8-H_e), 1.84-1.74 (m, 1H, 8-H_a); ^{13}C NMR ($CDCl_3$) δ 189.10 (C-5), 182.89 (C-12), 161.55 (C-4), 161.50 (C-6), 143.02(d, $^2J_{F,C\text{-}10a}$ = 18.9 Hz, C-10a), 136.78 (C-2), 135.93 (C-12a), 133.05 (C-11a), 131.23 (d, *J* = 3.6 Hz, C-6a), 120.89 (C-4a), 120.62 (C-1), 119.21 (C-3), 116.95 (d, $^3J_{F,C\text{-}11}$ = 8.4 Hz, C-11), 116.55 (C-5a), 94.55 (d, $J_{F,C\text{-}10}$ = 180.1 Hz, C-10), 71.56 (C-7), 66.34 (d, $^2J_{F,C\text{-}9}$ = 18.2 Hz, C-9), 58.41 (OMe-14), 56.92 (OMe-13), 32.79 (d, $^3J_{F,C\text{-}8}$ = 9.1 Hz, C-8); ^{19}F NMR ($CDCl_3$) δ -16.9 (dm, $J_{F,10\text{-}H}$ = 51.8 Hz). **10a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.54 (s, 1H, 6-OH), 7.97 (d, 1H, *J* = 7.8 Hz, 1-H), 7.90 (s, 1H, 11-H), 7.76 (dd, 1H, *J* = 7.8, 8.3 Hz, 2-H), 7.37 (d, 1H, *J* = 8.3 Hz, 3-Hz), 5.48 (dd, 1H, *J* = 48.4, 2.9 Hz, 10-H), 4.92 (t, 1H, *J* = 2.9 Hz, 7-H_e), 4.4-4.33 (m, 1H, 9-H), 4.07 (s, 3H, 13-OMe), 3.59 (s, 3H, 14-OMe), 2.53 (dt, 1H, *J* = 15.2, 2.9 Hz, 8-H_e), 2.13 (dm, 1H, *J* = 15.2 Hz, 8-H_a));^{13}C NMR ($CDCl_3$) δ 188.70 (C-5), 182.01 (C-12), 161.14 (C-4), 161.04 (C-6), 139.14 (d, $^2J_{F,C\text{-}10a}$ = 16.8 Hz, C-10a), 136.10 (C-2), 135.54 (C-12a), 132.60 (d, *J* = 2.5 Hz, C-6a), 130.93 (d, *J* = 3.8 Hz, C-11a), 120.56 (C-4a), 120.46 (d, $^3J_{F,C\text{-}11}$ = 4.0 Hz, C-11), 120.27 (C-1), 118.30 (C-3), 116.84 (d, *J* = 3.2 Hz, C-5a), 88.64 (d, $J_{F,C\text{-}10}$ = 173.4 Hz, C-10), 69.70 (C-7), 67.25 (d, $^2J_{F,C\text{-}9}$ = 27.0 Hz, C-9), 58.01 (OMe-14), 56.66 (OMe-13), 27.32 (C-8); ^{19}F NMR ($CDCl_3$) δ 3.04 (dd, $J_{F,10\text{-}H}$ = 48.4 Hz, $J_{F,9\text{-}H}$ = 9.5 Hz); MS (EI) m/z (relative intensity): 372 (M^+, 95), 342 (50), 341 (100), 273 (27), 242 (27).

6,9-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (11). A solution of **7** (0.9 g, 2.2 mmol), triethanolamine (80 mL), and Pd/C (10%, 15.0 mg) in ethanol (40 mL) was shaken on a Parr hydrogenation apparatus with a H_2 pressure of 31 psi for 3.5 h. The catalyst was removed by filtration through a celite pad, and to the filtrate were added EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined EtOAc extracts were washed with brine, dried, and filtered. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 9 : 1) to give **11** (0.8 g, 84%). mp 240-242 °C (lit 239-241 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.38 (s, 1H), 7.86 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.74 (t, *J* = 8.7 Hz, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 4.18 (m, 1H), 4.05 (s, 3H, OMe), 3.60-2.85 (m, 4H), 2.34-1.79 (m, 2H); MS m/z: 324 (M^+).

6-Hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (12). From alcohol **11**: To a solution of **11** (0.7 g, 2.2 mmol) in CH_2Cl_2 (80 mL) was added pyridinium chlorochromate (0.1 g, 4.3 mmol), and the mixture was vigorously stirred at r.t. for 2 h. The mixture was filtrated on celite pad and to the filtrate was added H_2O, and the aqueous layer was separated. The organic layer was washed with brine, dried, and filtered. The residue was purified by flash chromatography on silca gel (CH_2Cl_2/EtOAc, 4 : 1) to give **12** (0.6 g, 90 %).

From epoxide **7**: Using polyethylene equipment and under strict exclusion of moisture, to a cooled (0 °C) solution of HF/Pyr (7 : 3, 18 mL) was added the epoxide **7** (0.5 g, 1.6 mmol) in THF (30 mL) in one portion. The cooling bath was removed immediately, and the mixture was stirred under Ar at r.t. for 10 h. The reaction mixture was poured into ice water (50 mL) and extracted with CH_2Cl_2. The combined organic phases were evaporated to dryness, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/

EtOAc 98 : 2 to CH_2Cl_2/EtOAc 90 : 10) to give **12** (74%, 0.4 g) as a light yellow powder. mp 255-257 °C (lit 258-259 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.43 (s, 1H), 8.00 (dd, J = 7.5, 1.7 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.36 (dd, J = 7.6, 1.7 Hz, 1H), 4.08 (s, 3H), 3.68 (s, 2H), 3.24 (t, J = 6.1 Hz, 2H), 2.61 (t, J = 6.1 Hz, 2H); MS m/z: 322 (M^+).

(±)-6,9-Dihydroxy-4-methoxy-9-(trimethylsilyl)ethynyl -7,8,9,10-tetrahydronaphthacene-5,12-dione (13). Under a N_2 atmosphere, anhydrous $CeCl_3$ (0.4 g, 1.7 mmol) was stirred in THF (30 mL) at room temperature and cooled -78 °C. To the solution was added a mixture of (trimethylsilyl)ethynyllithium [prepared from (trimethyl)acetylene (0.2 mL, 1.7 mmol) and n-BuLi (1.3 mL, 1.3 mmol, 1.0 M in THF) in anhydrous THF (30 mL) at -40 °C for 30 min], and the mixture was stirred at -78 °C for 1 h. This mixture was added to a solution of **12** (98.0 mg, 0.3 mmol) in CH_2Cl_2 (40 mL) at -78 °C over 3 h. The mixture was stirred further for 2 h, quenched with 30 mL of sat. aqueous NH_4Cl, acidified with 1 N HCl, and extracted with CH_2Cl_2. The combined extract was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (MeOH/CH_2Cl_2 = 1 : 100) to give **13** (70.3 mg, 55%) as a yellow powder. mp 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (s, 1H, OH), 7.98 (dd, 1H, J = 8.0, 1.1 Hz, ArH), 7.75 (t, 1H, J = 8.0 Hz, ArH), 7.51 (s, 1H, ArH), 7.38 (dd, 1H, J = 8.0, 1.1 Hz, ArH), 3.99 (s, 3H, OMe), 3.28 (d, 1H, J = 17.9 Hz, 10-H_{eq}), 3.15 (d, J = 17.9 Hz, 10-H_{ax}), 2.90-3.02 (m, 2H), 2.15-2.17 (m, 2H), 0.14 (s, 9H, $3CH_3$). MS m/z: 420 (M^+).

(±)-9-Acetyl-6,9-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (14). A solution of **13** (80 mg, 0.2 mmol), yellow HgO (82.4 mg, 0.4 mmol), and 20% H_2SO_4 (1 mL) in THF (10 mL) was heated at reflux for 5 h. After cooling, the mixture was diluted with 1N HCl (10 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried and concentrated. The residue was chromatographed on silica gel (ether/CH_2Cl_2 = 1 : 20) to give **15** (73 mg, 92%) as a yellow powder: mp 219-221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.38 (s, 1H, OH), 7.96 (dd, J = 7.8, 1.3 Hz, ArH), 7.74 (t, 1H, J = 7.8 Hz, ArH), 7.48 (s, 1H, ArH), 7.35 (dd, J = 7.8, 1.3 Hz, ArH), 4.03 (s, 3H, OMe), 3.33 (d, 1H, J = 17.2 Hz, 10-H_{eq}), 2.91-3.08 (m, 2H), 2.80 (d, 1H, J = 17.2 Hz, 10-H_{ax}), 2.40 (s, 3H, 14-H), 1.90-2.13 (m, 2H). MS m/z: 366 (M^+).

(±)-11-Deoxydaunomycinone (15). A solution of **14** (97 mg, 0.3 mmol), bromine (19.5 mL, 0.4 mmol in CCl_4) and cat. amounts of AIBN in CCl_4 (30 mL) under N_2 was heated at reflux for 2 h. Additional bromine (9.9 mL, 0.2 mmol) was added and refluxing was continued for 1 h. The solvent was removed and the residue was added to a solution of Me_2SO (25 mL) with CF_3COONa (200 mg) and stirred under N_2 for 20 h. The reaction mixture was poured into H_2O and extracted with $CHCl_3$. The extracts were combined, washed with H_2O and dissolved in CF_3COOH (10 mL) and stirred at r.t. for 2 h. The solvent was removed and the residue dissolved in MeOH/THF (4 : 1, 20 mL) and stirred at r.t. for 4 h. The solution was poured into H_2O and extracted with $CHCl_3$. The extracts were combined, dried, and evaporated. The residue was purified by flash chromatography on a silica gel (CH_2Cl_2/MeOH, 99 : 1 to 97:3) to afford **15** (37.4 mg, 37%) as a yellow crystals: mp 210-213 °C (lit.[16] 213-215 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.69 (s,1H, OH), 8.01 (dd, 1H, J = 7.9, 1.1 Hz, ArH), 7.78 (t, 1H, J = 7.9 Hz, ArH), 7.62 (s, 1H, ArH), 7.41 (dd, 1H, J = 7.9, 1.1 Hz, ArH), 5.36 (ddd, 1H, J = 4.9, 4.8, 2.1 Hz, 7-H_{eq}), 3.98 (s, 3H, OMe), 3.68 (d, 1H, J = 4.8 Hz, 7-OH), 3.26 (d, 1H, J = 17.5 Hz, 10-H_{ax}), 3.01 (dd, 1H, J = 17.5, 2.4 Hz, 10-H_{eq}), 2.42 (s, 3H, 14-H), 2.35 (ddd, 1H, J = 15.0, 2.4, 2.1 Hz, 8-H_{eq}), 2.17 (dd, 1H, J = 15.0, 4.9 Hz, 8-H_{ax}).

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