1990, *112*, 4165.
7. Odashima, K.; Yagi, K.; Tohda, K.; Umezawa, Y. *Anal. Chem.* **1993,** *65*, 1074.
8. Jin, T.; Ichikawa, K. *J. Phys. Chem.* **1991,** *95*, 2601.
9. Yamada, A.; Murase, T.; Kikukawa, K.; Arimura, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans.* **1991,** *2*, 793.
10. Ahn, S.; Chang, S.-K.; Kim, T.; Lee, J. W. *Chem. Lett.* **1995**, 297.
11. Arnaud-Neu, F.; Collins, E. M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989,** *111*, 8681.
12. States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982,** *48*, 286.
13. Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993,** *34*, 7275.
14. Ahn, S.; Lee, J. W.; Chang, S.-K. *J. Chem. Soc., Perkin Trans.* **1996,** *2*, 79.
15. Kobayashi, K.; Asakawa, Y.; Kikuchi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1993,** *115*, 2648.
16. McConnell, J. In *The Theory of Nuclear Magnetic Relaxation in Liquid*; Cambridge University Press: Cambridge, 1987.
17. Popov, A. I. In *Modern NMR Techniques and Their Application in Chemistry*; Popov, A. I.; Hallenga, K. Eds.; Marcel Dekker Inc.: 1991; pp 485-520.
18. Gunther, H. *NMR Spectroscopy*, 2nd Ed.; John Wiley & Sons: 1995; p 344.
19. Boer, J. A. A. de; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1985,** *107*, 5347.

Synthesis of Novel 9-Fluoroanthracycline Derivatives

Young S. Rho*, Siho Park, Sun Y. Kim, Inho Cho, Chulhyun Lee†, Heun S. Kang‡, and Chaejoon Cheong†

Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea
†Magnetic Resonance Group, Korea Basic Science Institute, Taejon 305-333, Korea
‡R&D Center of Miwon Co., LTD, Icheon 467-810, Korea
Received September 12, 1997

Synthesis of novel 9-fluoroanthracyclines carrying L-fucose as a sugar component is described. Compound **3** containing a fluorine at the C-9 position was synthesized from an epoxide **2** and HF/Pyr (7 : 3). Bromination and hydrolysis of compound **3** resulted in synthesis of an aglycone, 9-fluoroanthracyclinone **6**. The α-(**1b**) and β-anomers (**1a**) of the final product were obtained in high yields by a coupling reaction with the L-fucose.

Introduction

A numerous anthracycline derivatives have been synthesized and tested for anticancer activity.[1] Nevertheless, the clinical use of anthracyclines requires further development of a more potent derivative with less cardiotoxicity.[2] Recently, it was reported[3] that introduction of fluorine to anthracycline increases anticancer activity. Derivatives of anthracycline showed either improved antitumor activity or reduced toxicity when fluorine was introduced at the C-1 and/or C-4 positions[4] of the D ring, the C-8[5] or C-14[6] positions of the A-ring, and the C-2' position of the glycone.[7]

We have synthesized a novel anthracycline derivative in which fluorine was introduced at the C-9 position on the aglycone A-ring. A sugar moiety, L-fucose, was subsequently coupled.[8] It was anticipated that the introduction of fluorine would result in higher affinity and increased binding to DNA.[9] Thus, we here describe the synthesis of anthracycline derivatives where fluorine and L-fucose were introduced.

*To whom correspondence should be addressed.

Results and Discussion

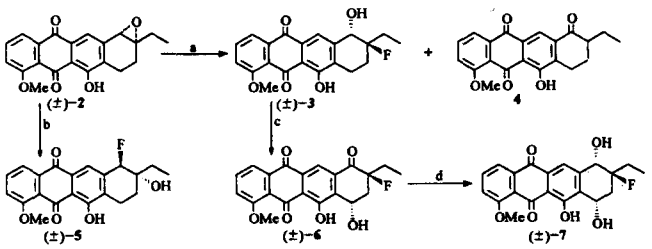
We have been using 3-phenylsulfonyl-1(3*H*)-isobenzofuranone derivatives[10] as Michael donors in constructing tetracyclic ring systems. However, we recently found[11] that the same results could be obtained by using newly synthesized 3-carbomethoxy-1(3*H*)-isobenzofuranone instead of these phthalide sulfones. Initially, a 95% yield of an epoxide (±)-**2**, (Scheme 1; yellow powder, mp 207-209 °C; lit.[10c] 208-211 °C) was obtained using methods previously described in the literature.[11] Hydrofluorination of epoxide **2** was then carried out with Olah's reagent[12] under various reaction conditions (Table 1) to obtain compound **3**, where a fluorine atom was introduced at the C-9 position. When Arcamone's method[5] was used (run 1), the yield was only 15% and the major reaction product was a ketone compound **4**. By optimizing the reaction time and the solvents (runs 2-5), the yield was raised to 50%: shorter reaction time and the use of methylene chloride as a solvent improved the yield. To improve the yield further, **2** was dissolved in chloroform and was added into HF/Pyr (7 : 3) in an ice-bath. The mixture was then kept at room temperature for 5 minutes to complete the reaction (run 6). Using this method, a yield

more than 80% of compound (±)-**3** was obtained. The NMR peak splitting of C-9 ($J_{F,C\text{-}9}$=183 Hz) confirmed that fluorine was introduced on the correct C-9 position, and from the scalar couplings ($^3J_{F,C\text{-}7}$=11.6 Hz, $^3J_{F,8\text{-}H}$=9.5, 6.5 Hz), it was concluded that the fluorine was *equatorial*.[13] From NMR, It was known that a small amount of *cis* compound of **3** was also obtained.

Reducing the HF concentration slowed the reaction rate and decreased the yield of **3** substantially. However, with longer reaction time (run 7), new compound (±)-**5** was synthesized where the fluorine was introduced at the C-10 position ($J_{F,C\text{-}10}$=181 Hz), although the yield was low (12%). This occurs because the epoxide ring is on the benzylic position unlike the substrates of the Arcamone reaction. Consequently, the hydrofluorination had to be accomplished using very short reaction times in $CHCl_3$. Since fluorine attack to the epoxide ring is characteristically of a S_N2 type,[14] the fluorine was introduced at a more hindered position under the acidic conditions (run 6) and was introduced at a less hindered position under the basic conditions[15] (run 7).

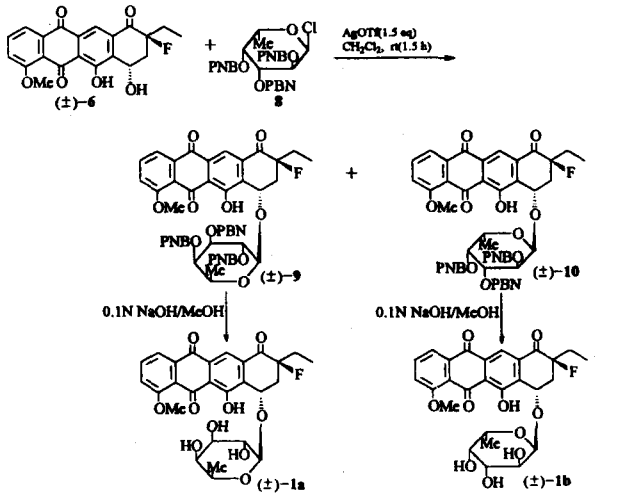
To hydroxylate C-7 of compound **3** in a *pseudoaxial* form and to oxidize 10-OH, the obtained **3** was dissolved in CCl_4 and then refluxed with AIBN (Scheme 1). This was followed by addition of Br_2 dissolved in CCl_4, and then hydrolysis.[16] With this method, product (±)-**6** was obtained with a 71% yield in racemic mixture. We also confirmed that the OH was introduced at the C-7 position as a *pseudoaxial* form from proton scalar coupling constants ($^3J_{7\text{-}H,8\text{-}H}$= 5.8, 4.2 Hz). An extraordinary long-range "W"-type coupling ($^4J_{F,7\text{-}H}$=1.6 Hz) was observed, further confirming the *pseudoaxial* introduction of 7-OH. In this reaction, the hydroxyl group at C-10 was oxidized (193.4 ppm, $^2J_{F,C\text{-}10}$=20 Hz) probably due to the effect of hydrobromic acid generated during the bromination process. When we attempted to synthesize compound **7** without oxidizing the C-10 hydroxyl group using NBS·AIBN for bromination, no reaction was produced. When poly(4-vinylpyridinium bromide perbromide)[5,17] was used, only compound **6** was occurred (14% yield). LS-selectride[18] was used at −78 °C to stereoselectively reduce the C-10 position of 6 thereby making compound (±)-**7**, but the yield turned out to be relatively low (25%). The OH substitution at C-10 was confirmed by vicinal and long range scalar couplings ($^3J_{F,10\text{-}H}$=21.5 Hz, $^4J_{F,10\text{-}OH}$=1.9 Hz, $^3J_{10\text{-}H,10\text{-}OH}$=10.7 Hz).

The final products **1** were synthesized by coupling the obtained compound **6** and a fucose (Scheme 2). L-fucose was treated with p-nitrobenzoyl chloride in pyridine.[19] This fucopyranose was used in the glycosidation of **6**. Coupling attempts under various conditions using the glycosidic promotors, TMSOTf[20] or $SnCl_4$,[21] were unsuccessful. Therefore,



Scheme 1. (a) HF/Pyr(7 : 3)/$CHCl_3$, 0 °C, rt, 5 min, (b) HF/Pyr (44 : 56)/$CHCl_3$, rt, 24 hr, (c) Br_2, AIBN/CCl_4, reflux (1.5 hr), 71%, (d) LS-selectride/THF, −78 °C (2 hr), rt (1 hr), 15%.

in order to use the Koenigs-Knorr coupling method, the fucopyranose was converted to fucopyranosyl chloride **8** (1-H: 6.94→6.59 ppm upfield shift) by substituting C-1 with chlorine using α,α-dichloromethyl methyl ether and zinc chloride.[22] The coupling of compounds **6** and **8** was attempted without success using silver triflate[23] in THF, because a highly viscous slurry was formed probably due to formation of an oxonium intermediate from the oxygen of THF and AgOTf.[24] To remedy this, methylene chloride/ether was used as the solvent instead of THF. Compounds **6** and **8** were dissolved in methylene chloride at room temperature and a mixture of AgOTf and ether was added. After completion of the reaction, two anomeric mixtures, compounds (±)-**9** (57%) and (±)-**10** (10%), were separated by column chromatography. Without confirming the structures, the fucose PNB groups on each of the two products were hydrolyzed using 0.1 N-NaOH.[25] The final products, (±)-**1a** (87%) and (±)-**1b** (84%), were purified by HPLC using a



Scheme 2.

Table 1. The hydrofluorination of epoxy compound **2**

Run	Reagents (%)	Solvents	Conditions	Products (isolated yield)
1	HF/Pyr (70/30)	THF	0 °C (50 min)	**3** (15%), **4** (68%)
2	HF/Pyr (70/30)	THF	0 °C, rt (8 hr)	**4** (76%)
3	HF/Pyr (70/30)	CH_2Cl_2	−10 °C (4 hr), rt (3 hr)	**3** (6%), **4** (63%)
4	HF/Pyr (70/30)	CH_2Cl_2	−10 °C (15 min)	**3** (44%), **4** (45%)
5	HF/Pyr (70/30)	CH_2Cl_2	−10 °C (10 min)	**3** (50%), **4** (40%)
6	HF/Pyr (70/30)	$CHCl_3$	0 °C, rt (5 min)	**3** (80%), **4** (16%)
7	HF/Pyr (44/56)	$CHCl_3$	rt (24hr)	**3** (10%), **4** (11%), **5** (12%)

C18 column. From NMR data, the two compounds were found to be anomeric isomers. Compound **1a** was confirmed to be a β-anomer (1'-H, δ= 4.72 ppm, $J_{1'\text{-H},2'\text{-H}}$=7.7 Hz), and **1b** an α-anomer (1'-H, δ=5.43 ppm, $J_{1'\text{-H},2'\text{-H}}$=4.0 Hz). The conformation of the fluorine, which was introduced during synthesis of **3**, was maintained as *equatorial* ($^3J_{F,C\text{-}7}$=14 Hz for **1a**, 13 Hz for **1b**) throughout the synthesis of the final products. Detailed analysis of the structure will be published elsewhere.[26]

Experimental

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 recorded on a JEOL JMX-DX 300 spectrometer (EI and FAB^+) and on a VG QUATTRO spectrometer (ESI). UV/VIS spectra were recorded on a Beckman DU 7500 spectrophotometer. Optical rotations were recorded on a Perkin-Elmer polarimeter 241. Melting point were obtained on a Büchi 510 melting point apparatus and were uncorrected. Products were purified by flash column chromatography on a silica gel (60-200 mesh), HPLC (LCMI-WATERS), MPLC (YFLC 5404-FC) and/or by recrystallization.

(±)-6,10-Dihydroxy-9-ethyl-9-fluoro-4-methoxy-7,8,9,10-tetrahydronaphthacen-5,12-dione (3). 9-Ethyl-6-hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacen-5,10,12-trione (4). Using polyethylene equipment and under strict exclusion of moisture, to a cooled (0 °C) solution of HF/Pyr (7:3, 30 mL) was added the epoxide **2** (0.95 g, 2.71 mmol) in $CHCl_3$ (30 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 (30 mL) and extracted with CH_2Cl_2. The combined organic phases were evaporated to dryness, the residure was purified by flash chromatography on a silica gel (CH_2Cl_2/EtOAc 2:98 → CH_2Cl_2/EtOAc 10:90) to give **3** (80%, 0.80 g) as a dark yellow powder and **4** (16%, 0.15 g) as a light yellow powder. **3**: mp 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.24 (s, 1H, 6-OH), 7.84 (d, 1H, *J*=7.7 Hz, 1-H), 7.77 (s, 1H, 11-H), 7.70 (dd, 1H, *J*=8.4, 7.7 Hz, 2-H), 7.33 (d, 1H, *J*=8.4 Hz, 3-H), 4.71 (dd, 1H, *J*=8.4, 5.0 Hz, 10-H), 4.05 (s, 3H, OMe), 2.86 (t, 2H, *J*=6.6 Hz, 7-H_2), 2.59 (d, 1H, *J*=5.0 Hz, 10-OH), 2.20-2.04 (m, 2H, 8-H_2), 2.02-1.94 (m, 1H, 13-H_a), 1.76-1.62 (m, 1H, 13-H_b), 1.07 (dd, 3H, *J*=7.7, 7.3 Hz, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.67 (C-5), 182.17 (C-12), 160.79 (C-4), 160.26 (C-6), 144.11 (C-10a), 135.82 (C-6a), 135.64 (2-CH), 133.17 (C-12a), 130.32 (C-11a), 120.63 (C-4a), 120.14 (1-CH), 119.23 (C-11), 118.10 (3-CH), 114.92 (C-5a), 96.38 (d, $J_{F,C\text{-}9}$=183 Hz, 9-CF), 71.37 (d, $^2J_{F,C\text{-}10}$ =31 Hz, 10-CH), 56.62 (OMe), 26.36 (8-CH_2), 26.13 (13-CH_2), 20.76 (d, $^3J_{F,C\text{-}7}$=11 Hz, 7-CH_2), 6.63 (14-CH_3); MS: m/z=370 (M^+, 67.9%), 352 (37), 293 (96.6), 149 (100).

4: mp 208-210 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.37 (s, 1H, OH), 8.33 (s, 1H, ArH), 7.96 (d, 1H, *J*=8.1 Hz, ArH), 7.77 (t, 1H, *J*=8.1 Hz, ArH), 7.37 (d, 1H, *J*=8.1 Hz, ArH), 4.08 (s, 3H, OMe), 3.22 (dt, 1H, *J*=18.3, 5.1 Hz), 2.89 (ddd, 1H, *J*=13.9, 9.5, 5.1 Hz), 2.47 (dddd, 1H, *J*=18.3, 9.5, 4.4, 1.5 Hz), 2.32 (dddd, 1H, *J*=18.3, 9.5, 5.1, 4.4 Hz), 2.02-1.90 (m, 2H), 1.63-1.53 (m, 1H), 1.03 (t, 3H, *J*=7.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.91, 188.91, 181.88, 161.01, 160.69, 140.28, 137.34, 136.17, 135.95, 130.31, 120.71, 120.30, 119.21, 118.30, 116.93, 56.67, 48.41, 26.34, 22.14, 22.03, 11.34; MS: m/z=350 (M^+, 83%), 322(100), 304(32), 266(27).

(±)-6,9-Dihydroxy-9-ethyl-10-fluoro-4-methoxy-7,8,9,10-tetrahydronaphthacen-5,12-dinone (5). Reaction between **2** and the HF/Pyr (44:56) in $CHCl_3$ was carried out for 24 h as described for **3**. The residue was purified by flash chromatography on a silica gel to give **3** (10%), **4** (11%) and **5** (12%) as a redish yellow powder. **5**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.35 (s, 1H, OH), 7.97 (d, 1H, *J*=7.8 Hz, ArH), 7.86 (s, 1H, ArH), 7.75 (t, 1H, *J*=7.8 Hz, ArH), 7.36 (d, 1H, *J*=7.8 Hz, ArH), 5.26 (d, 1H, *J*=49.8 Hz, 10-H), 4.08 (s, 3H, OMe), 2.92-2.88 (m, 2H), 2.05 (ddd, 1H, *J*=14.7, 6.8, 5.9 Hz), 1.91 (ddd, 1H, *J*=14.7, 7.8, 6.8 Hz), 1.80 (dddd, 1H, *J*=14.7, 7.8, 6.8, 2.0 Hz), 1.64 (ddd, 1H, *J*=14.7, 8.8, 2.0 Hz), 1.07 (t, 3H, *J*=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 188.96, 182.26, 160.95, 160.35, 140.44 (d), 135.93, 134.01, 130.51, 128.87, 120.78, 120.26, 119.49, 119.44, 118.12, 115.63, 92.20 (d), 71.81 (d), 56.70, 27.84, 20.70, 6.56; MS: m/z=370 (M^+, 67.9%), 350(47.2), 322(54.3), 305(36.8), 293(96.6), 149(100).

(±)-6,7-Dihydroxy-9-ethyl-9-fluoro-4-methoxy-7,8,9,10-naphthacen-5,10,12-trione (6). To a hot solution of **3** (0.80 g, 2.16 mmol) and AIBN (7.10 mg) in dry CCl_4 (200 mL) was added dropwise a solution of Br_2 (0.22 mL, 4.32 mmol) in CCl_4 (30 mL) under N_2. The mixture was heated at reflux further for 1.5 h. The reaction mixture was cooled and washed with 10% $NaHSO_3$. The organic phase was evaporated to dryness under reduced pressure, and the residue was taken up in THF-H_2O (1:1, 200 mL) and stirred for 2 h at r.t. The THF was removed, and the mixture was extracted with CH_2Cl_2. The combined organic layers were successively washed with $NaHCO_3$ solution, H_2O and brine, and were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on a silica gel (CH_2Cl_2/EtOAc 10:90 → CH_2Cl_2/EtOAc 20:80), and by HPLC with a prep pak column (buffer soln, CH_3CN 35%: 0.02 M NaH_2PO_4 65%: Et_3N 0.1%; flow rate, 10 mL/min) to give **6** (0.59 g, 71%) as a dark yellow powder. mp 232-234 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.81 (s, 1H, 6-OH), 8.43 (s, 1H, 11-H), 8.05 (d, 1H, *J*=8.8 Hz, 1-H), 7.85 (dd, 1H, *J*=8.8, 7.8 Hz, 2-H), 7.44 (d, 1H, *J*=7.8 Hz, 3-H), 5.52 (ddd, 1H, *J*=5.8, 4.2, 1.6 Hz, 7-H_{eq}), 4.14 (s, 3H, OMe), 3.58 (s, 1H, 7-OH), 2.77 (ddd, 1H, *J*=14.6, 9.5, 5.8 Hz, 8-H_{eq}), 2.59 (ddd, 1H, *J*=14.6, 6.5, 4.2 Hz, 8-H_{ax}), 2.19-2.09 (m, 2H, 13-H_2), 1.09 (dd, 3H, *J*=7.8, 6.8 Hz, 14-H_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.37 (d, $^2J_{F,C\text{-}10}$=20 Hz, C-10), 188.86 (C-5), 181.34 (C-12), 161.41 (C-4), 160.77 (C-6), 137.70 (C-6a), 136.69 (2-CH), 135.84 (C-12a), 135.03 (C-10a), 132.61 (C-11a), 120.62 (C-4a), 120.61 (1-CH), 119.41 (C-5a), 118.51 (3-CH), 117.40 (11-CH), 95.52 (d, $J_{F,C\text{-}9}$=183 Hz, 9-CF), 62.24 (d, $^3J_{F,C\text{-}7}$=12 Hz, 7-CH), 56.78 (OMe), 37.66 (d, $^2J_{F,C\text{-}8}$=22 Hz, 8-CH_2), 28.52 (d, $^2J_{F,C\text{-}13}$=23 Hz, 13-CH_2), 6.87 (14-CH_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ

– 162.30 (m, 1F); FT-IR (KBr, pellet): ν=3514, 2924, 1714, 1665, 1623, 1581, 1454, 1384, 1293, 1236, 1194, 1039, 997, 969, 835, 800, 737 cm^{-1}; UV (MeOH): λ_{max} (logε)=211(0.88), 238 (0.92), 526 (0.01); MS (ESI, negative, MeOH): m/z=383 $[M-H]^{-1}$.

(±)-9-Ethyl-9-fluoro-4-methoxy-6,7,10-trihydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione (7). To a solution of LS-selectride (0.16 mL, 0.16 mmol, 1.0 M in THF) which was cooled to – 78 °C under N_2, was added **6** (50.0 mg, 0.13 mmol) in THF (15 mL), and the mixture was stirred further for 2 h. The cooling bath was removed and the mixture was heated at reflux for 1 h. After adding H_2O, EtOAc, and K_2CO_3 successively, the organic layer was separated. The residue was chromatographed on a silica gel (CH_2Cl_2/EtOAc 10 : 90 → CH_2Cl_2/EtOAc 20 : 80) to give **7** (12.57 mg, 25%) as a redish yellow powder. mp 193-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.24 (s, 1H, OH), 8.07 (s, 1H, ArH), 7.95 (d, 1H, *J*=7.8 Hz, ArH), 7.78 (t, 1H, *J*=7.8 Hz, ArH), 7.38 (d, 1H, *J*=7.8 Hz, ArH), 5.33 (dd, 1H, *J*=8.8, 6.8 Hz, 7-H), 4.65 (dd, 1H, *J*=21.5, 10.7 Hz, 10-H), 2.76 (ddd, 2H, *J*=14.6, 6.8, 4.9 Hz, 8-H_2), 2.31 (dd, 1H, *J*=10.7, 2.0 Hz, 10-OH), 2.09-1.86 (m, 3H), 1.08 (dd, 3H, *J*=7.8, 6.8 Hz, 14-H); MS: m/z=386 (M^+).

2,3,4-Tri-*O*-(*p*-nitrobenzoyl)-α-L-fucopyranosyl chloride (8). To a solution of 6-deoxy-L-galactose (0.5 g, 3.05 mmol) in dry pyridine (30 mL) which was cooled to 0 °C under N_2, was added *p*-nitrobenzoyl chloride (3.39 g, 18.28 mmol), and the mixture was stirred for 16 h to afford 1,2,3,4-Tetra-*O*-(*p*-nitrobenzoyl)-α-L-fucopyranose (2.16 g, 93 %) as a white powder. mp 239-241 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, 4H, *J*=8.8 Hz, ArH), 8.29 (dd, 4H, *J*=8.8, 6.6 Hz, ArH), 8.17 (d, 4H, *J*=8.8 Hz, ArH), 7.99 (t, 4H, *J*=8.8 Hz, ArH), 6.94 (d, 1H, *J*=3.7 Hz, 1-H), 6.67 (dd, 1H, *J*=11.0, 2.9 Hz), 6.00 (dd, 1H, *J*=10.3, 3.7 Hz), 5.94 (d, 1H, *J*=2.9 Hz), 4.71 (q, 1H, *J*=6.6 Hz, 5-H), 1.39 (d, 3H, *J*= 6.6 Hz, 6-H); ^{13}C NMR ($CDCl_3$): δ 164.18, 163.85, 163.72, 162.89, 151.24, 150.97, 134.07, 133.88, 133.77, 133.60, 131.06, 130.79, 124.11, 123.78, 91.43, 72.09, 69.55, 68.24, 68.07, 16.25; MS (FAB^+): m/z=760 (M^+).

To a solution fucopyranose (2.0 g, 2.63 mmol) and α,α-dichloromethyl methyl ether (1.31 mL, 14.46 mmol) in CH_2Cl_2 (90 mL), cooled to 0 °C under N_2, was added $ZnCl_2$ (11.57 mL, 11.57 mmol, 1.0 M in Et_2O), and the mixture was stirred for 1 h at r.t. The residue was chromatographed on a silica gel (CH_2Cl_2/Hexane 2 : 98) to afford **8** (1.29 g, 78%) as a white powder. mp 137-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, 2H, *J*=8.8, 2.2 Hz, ArH), 8.26 (dd, 4H, *J*=8.8, 2.2 Hz, ArH), 8.16 (m, 4H, ArH), 7.97 (dd, 2H, *J*=8.8, 2.2 Hz, ArH), 6.59 (d, 1H, *J*=3.7 Hz, 1-H), 6.06-6.02 (m, 1H), 5.87 (d, 1H, *J*=4.4 Hz), 5.84 (dd, 1H, *J*=10.3, 3.7 Hz), 4.78 (q, 1H, *J*=6.6 Hz), 1.38 (d, 3H, *J*=6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 164.04, 163.77, 163.55, 151.13, 151.05, 150.86, 133.90, 133.63, 131.09, 131.01, 130.70, 124.06, 123.81, 123.70, 91.24, 71.90, 69.36, 69.03, 68.32, 15.86; MS (FAB^+): m/z=629 (M^+).

7-*O*-(β/α-L-Fucopyranosyl)-(±)-9-ethyl-9-fluoro-6-hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacen-5,10,12-trione (1a/1b). A solution of AgOTf (47.0 mg, 0.18 mmol) in ether (3 mL) was added to a mixture of fucopyranosyl chloride **8** (98.0 mg, 0.16 mmol) and **6** (50.0 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) with stirring at r. t. and stirred further for 1.5 h under Ar. The mixture was diluted with CH_2Cl_2 (50 mL), and washed with satd $NaHCO_3$ (50 mL). The seperated organic layer was dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography (CH_2Cl_2/EtOAc 1 : 9) → EtOAc/Hexane 1 : 1) gave **9** (72.51 mg, 57%, mp 260 °C, dec) as a dark yellow powder and 10 (12.72 mg, 10%, mp 205-207 °C) as a yellow powder. **9** and **10** was used for the next reaction without further confirming the structures.

0.1 M NaOH (0.9 mL) was added to a solution of **9** (20 mg, 0.02 mmol) in CH_2Cl_2 (20 mL) and MeOH (20 mL) with stirring at 0 °C under Ar. The deep purple solution produced was stirred 40 min at 0 °C. To a mixture was added glacial AcOH till the purple solution was changed to bright orange. The reaction mixture was extracted with EtOAc. The extract was washed with satd NaCl, dried with $MgSO_4$, and evaporated in vacuo. Purification by HPLC with a Prep Pak symmetry C_{18} 40×100 mm column (Buffer soln: CH_3CN, 35%; 0.06 M Na_2HPO_4, 39%; citric acid, 26%; Et_3N, 0.05%) gave **1a** (9.43 mg, 87%) as orange crystals. From **10** by the same method was obtained **1b** (9.10 mg, 84%) as orange crystals. **1a**: mp 132-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$/CD_3OD): δ 8.37 (s, 1H, 11-H). 7.99 (d, 1H, *J*=7.8 Hz, 1-H), 7.83 (dd, 1H, *J*=8.4, 7.8 Hz, 2-H), 7.44 (d, 1H, *J*= 8.4 Hz, 3-H), 5.36 (m, 1H, 7-H), 4.72 (d, 1H, *J*=7.8 Hz, 1'-H), 4.09 (s, 3H, OMe), 3.77 (dq, 1H, *J*=6.7, 1.1 Hz, 5'-H), 3.71 (dd, 1H, *J*=3.3, 1.1 Hz, 4'-H), 3.64 (dd, 1H, *J*=9.5, 3.3 Hz, 3'-H), 3.54 (dd, 1H, *J*=9.5, 7.8 Hz, 2'-H), 3.11 (ddd, 1H, *J*=14.5, 5.6, 2.2 Hz, 8-H_{eq}), 2.56 (ddd, 1H, *J*=14.5, 10.6, 5.0 Hz, 8-H_{ax}) 2.15 (m, 2H, 13-H_2), 1.40 (d, 3H, *J*=6.7 Hz, 5'-Me), 1.04 (t, 3H, *J*=7.8 Hz, 14-H_3); ^{13}C NMR (150 MHz, $CDCl_3$/CD_3OD): δ 194.75 (d, $^2J_{F,C-10}$=18 Hz, C-10), 188.50 (C-5), 181.39 (C-12), 161.15 (C-4), 160.76 (C-6), 136.75 (2-CH), 135.33 (C-6a), 135.26 (C-12a), 134.29 (C-10a), 132.95 (C-11a), 120.38 (1-CH), 120.14 (C-4a), 119.53 (C-5a), 118.54 (3-CH), 116.94 (11-CH), 105.11 (1'-CH), 95.64 (d, $J_{F,C-9}$=187 Hz, 9-CF), 73.50 (3'-CH), 71.73 (2'-CH), 71.08 (4'-CH), 70.84 (5'-CH), 70.59 (d, $^3J_{F,C-7}$=14 Hz, 7-CH), 56.57 (OMe), 36.88 (d, $^2J_{F,C-8}$=22 Hz, 8-CH_2), 29.12 (d, $^2J_{F,C-13}$=23 Hz, 13-CH_2), 16.22 (5'-Me), 6.36 (14-CH_3); ^{19}F NMR (282 MHz, $CDCl_3$/CD_3OD): δ – 161.05 (m, 1F); MS (ESI, negative, MeOH): m/z=529 $[M-H]^{-1}$.

1b: mp 130-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$/CD_3OD): δ 8.36 (s, 1H, 11-H), 7.97 (d, 1H, *J*=7.7 Hz, 1-H), 7.81 (dd, 1H, *J*=8.3, 7.7 Hz, 2-H), 7.42 (d, 1H, *J*=8.3 Hz, 3-H), 5.43 (d, 1H, *J*=4.0 Hz, 1'-H), 5.33 (m, 1H, 7-H), 4.07 (s, 3H, OMe), 4.05 (m, 1H, 5'-H), 3.86 (dd, 1H, *J*=10.0, 4.0 Hz, 2'-H), 3.76 (dd, 1H, *J*=2.9, 2.2 Hz, 4'-H), 3.62 (dd, 1H, *J*=10.0, 2.9 Hz, 3'-H), 2.74 (m, 2H, 8-H_2), 2.26 (m, 2H, 13-H_2), 1.32 (d, 3H, *J*=6.5 Hz, 5'-Me), 0.97 (t, 3H, *J*=7.4 Hz, 14-H_3); ^{13}C NMR (150 MHz, $CDCl_3$/CD_3OD): δ 193.71 (d, $^2J_{F,C-10}$=18 Hz, C-10), 188.49 (C-5), 181.32 (C-12), 161.23 (C-4), 160.58 (C-6), 136.83 (2-CH), 135.49 (C-6a), 135.23 (C-12a), 134.12 (C-10a), 133.02 (C-11a), 120.39 (1-CH), 120.12 (C-4a), 119.60 (C-5a), 118.60 (3-CH), 117.09 (11-CH), 101.50 (1'-CH), 95.17 (d, $J_{F,C-9}$=187 Hz, 9-CF), 71.49 (4'-CH), 70.87 (3'-CH), 70.60 (d, $^3J_{F,C-7}$=13 Hz, 7-CH), 69.10 (2'-CH), 67.56 (5'-CH), 56.60 (OMe), 37.81 (d, $^2J_{F,C-8}$=22 Hz, 8-CH_2), 29.19 (d, $^2J_{F,C-13}$=23 Hz, 13-CH_2), 16.08 (5'-Me), 6.90 (14-CH_3); ^{19}F NMR (282 MHz, $CDCl_3$/CD_3OD): δ – 161.05 (m, 1F); MS (ESI, negative, MeOH): m/z=529 $[M-H]^{-1}$

Acknowledgment. The authors thank Dr. Sung-Eun Yoo of KRICT for his helpful comments. This work was supported by the Korea Sanhak Foundation (1995) and the Basic Science Research Institute Program (BSRI-96-3431) and by the Koyu-program (1997) of the Korea Basic Science Institute (to C.C.).

References

1. Cumulative NCE Introduction Index 1983-1993, Annual Rep. Chem. 1994; 375.
2. (a) Weiss, R. B. *Semin. Oncol.* **1993,** *19*, 670. (b) Mross, K. *Eur. J. Cancer* **1991,** *27*, 1542.
3. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990,** *29*, 1320.
4. Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987,** *52*, 713.
5. Giolitti, A.; Guidi, A.; Pasqui, F.; Pestellini, V.; Arcamone, F. *Tetrahedron Lett.* **1992,** *33*, 1637.
6. (a) Matsumoto, T.; Ohsaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1987,** *28*, 4419. (b) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Terashima, S. *Tetrahedron Lett.* **1989,** *30*, 4259.
7. (a) Tsuchiya, T.; Takagi, Y.; Ok, K.; Umezawa, S.; Takeuchi, T.; Wako, M.; Umezawa, H. *J. Antibiot.* **1986,** *39*, 731. (b) Ok, K.; Takagi, Y.; Tsuchiya, T.; Umezawa, S.; Umezawa, H. *Carbohydr. Res.* **1987,** *169*, 69.
8. Flowers, H. M. *Adv. Carbohydr. Chem. Biochem.* **1981,** *39*, 279.
9. (a) Gresh, N.; Pullman, B.; Arcamone, F.; Menozzi, M.; Tonani, R. *Mol. Pharmacol.* **1989,** *35*, 251. (b) Wang, A. H. J.; Ughetto, G.; Quigley, G. J.; Rich, A. *Biochemistry* **1987,** *26*, 1152.
10. (a) Hauser, F. M.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1989,** *54*, 5110. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978,** *43*, 178. (c) Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984,** *40*, 4711.
11. (a) Rho, Y. S.; Yoo, J. H.; Baek, B. N.; Kim, C. J.; Cho, I. H. *Bull. Korean Chem. Soc.* **1996,** *17*, 946. (b) Rho, Y. S.; Park, S. H.; Kwon, Y. J.; Yoo, J. H. *J. Korean Chem. Soc.* **1996,** *40*, 519.
12. (a) Olah, G. A.; Nojima, M. *Synthesis* **1973**, 785. (b) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979,** *44*, 3872. (c) Wilkinson, J. A. *Chem. Rev.* **1992,** *92*, 505-519. (d) Mascaretti, O. A. *Aldrichimica Acta* **1993,** *26*, 47.
13. Wray, V. *J. Chem. Soc., Perkin II* **1976**, 1598.
14. (a) Suga, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1990,** *46*, 4247. (b) Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1988,** *53*, 1026.
15. Olah, G. A.; Meidar, D. *Israel J. Chem.* **1978,** *17*, 148.
16. Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981,** *103*, 4251.
17. Sket, B.; Zupan, M. *J. Org. Chem.* **1986,** *51*, 929.
18. Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976,** *41*, 3383.
19. Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977,** *42*, 3653.
20. Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986,** *59*, 423.
21. Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Yoshimoto, A.; Ishikura, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *Tetrahedron Lett.* **1984,** *25*, 3355.
22. Pozsgay, V. *J. Am. Chem. Soc.* **1995,** *117*, 6673.
23. (a) Adams, N.; Blake, C.; Broadhurst, M. J.; Bushnell, D. J.; Hassall, C. H.; Hartmann, H. R.; Keech, E.; Stratton, A. R.; Thomas, G. J. *J. Med. Chem.* **1990,** *33*, 2375. (b) Idem. *Ibid.* **1990,** *33*, 2380.
24. Schmidt, R. R.; Klotz, W. *Synlett* **1991**, 168.
25. Pasqui, F.; Canfarini, F.; Giolitti, A.; Guidi, A.; Pestellini, V.; Arcamone, F. *Tetrahedron* **1996**, *52*, 185.
26. Lee, C. *et al.* In preparation.