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Anthracycline glycosides of 2,6-dideoxy-2-fluoro-α-L-talopyranose

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Abstract—The methyl β-glycoside of the title sugar, obtained from 2-deoxy-2-fluoro-β-D-glucopyranose tetraacetate by a sequence with detailed characterization of all intermediates, was converted by acetolysis–bromination into 3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl bromide, coupling of which with (7*S*,9*S*)-4-demethoxydaunomycinone afforded the 3,4-diacetate of 4-demethoxy-9-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**19**). The antitumor-active **19** was converted by way of its 14-bromo derivative into the 14-hydroxy analogue, the antitumor-active 4-demethoxyadriamycinone glycoside **21**.

Keywords: Fluoro sugars; Anthracycline glycosides; Glycosylation; Adriamycin analogues

1. Introduction

Analogues of the natural anthracycline antibiotics daunorubicin and doxorubicin having diminished toxicity and/or enhanced antitumor activity have been targets of synthesis in this laboratory[1] and others.[2–7] Replacement of the 3′-amino group by hydroxyl via semisynthesis through appropriate glycosylation of daunomycinone has yielded products of lower toxicity,[8] and hydroxylation of the aglycon at the 14-position has permitted conversion into doxorubicin analogues of enhanced antitumor activity.[9] Introduction of an axially oriented halogen atom at the 2-position of the sugar has afforded products demonstrating higher activity,[10,11] the synthesis of which has been achieved via glycal intermediates for the 2′-chloro,[11] 2′-bromo-,[11] and 2′-iodo[10] structures; alternative strategy has been required to obtain the 2′-fluoro compounds.[12,13]

Although daunomycinone and adriamycinone, the aglycons of the natural antibiotics, possess a methoxy group at the 4-position of the aromatic ring, this group does not appear to play any essential role in the biological activity of their 7-glycosylated derivatives.[12,14,15] Envisaging the target of a fully synthetic analogue incorporating attributes favorable to high activity, a component aglycon lacking the 4-methoxy group would be easier to synthesize, as there would be no requirement for a regiospecific step to correctly orient the methoxy group. We have already demonstrated[12,14] that a chiral glycon can be used as a resolving agent in coupling to synthetic, racemic 4-demethoxydaunomycinone[16] to furnish separable, enantiomerically pure diastereomers, one of which has the stereochemistry of the natural aglycon.

Here we report the glycosidic attachment to the 9-position of (+)-(7*S*,9*S*)-4-demethoxydaunomycinone (idarubicinone)[17] of a 2,6-dideoxy-2-fluoro-α-L-talopyranosyl group, to afford a daunorubicin analogue (**19**), and its subsequent conversion via hydroxylation at the 14-position into the corresponding doxorubicin analogue **21**. Compounds **19** and **21** are 4-demethoxy-3′-hydroxy-3′-deamino-2′axial-fluoro analogues of the parent natural antibiotics. Synthesis of the fluoro sugar glycon follows essentially the steps of a concise synthesis earlier reported,[18] but gives detailed characterization of all intermediates in both anomeric forms.

2. Results and discussion

The previous report[18] described the synthesis of methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside (**15**) in 27%

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net yield by a nine-step sequence starting from 2-deoxy-2-fluoro-β-D-glucopyranose tetraacetate (**1**), a compound accessible[19] in two steps from D-mannose. Compound **15**, the glycon precursor required for the target anthracycline glycosides, was prepared essentially by the route previously used,[18] but in the present work the anomeric mixtures obtained in the intermediate steps were resolved and each of the products was characterized in detail (Scheme 1).

Acid-catalyzed methanolysis of **1**, followed by benzylidenation of the resultant methyl 2-deoxy-2-fluoro-α,β-glucopyranoside (**2**), afforded 90% of a 2:3 mixture of methyl 4,6-*O*-benzylidene-2-deoxy-α- and β-D-glucopyranosides (**3** and **4**), which were separated chromatographically and each obtained crystalline. The levorotatory β anomer was characterized by detailed ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy; the dextrorotatory α anomer had properties concordant with those already reported.[18]

Oxidation of the mixture of anomers **3** and **4** with pyridinium dichromate gave 96% of the corresponding glycos-3-ulosides **5** and **6**, which were separated chromatographically to give the individual anomers, again both crystalline and characterized by detailed NMR studies; the α anomer was described in the earlier report.[18] Borohydride reduction of the mixed glycos-3-ulosides **5** and **6** proceeded essentially stereospecifically by predictable 'topside' attack to give 83% of the corresponding mixed allosides **7** and **8**, which on chromatographic resolution furnished the less-polar, levorotatory β anomer **8** and the earlier reported[18] dextrorotatory α anomer **7**, both crystalline. Conventional acetylation of the individual anomers **7** and **8** gave the corresponding 3-acetates **9** and **10**.

Treatment of α alloside **9** with *N*-bromosuccinimide in boiling carbon tetrachloride afforded 88% of the crystalline, dextrorotatory methyl 3-*O*-acetyl-4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-allopyranoside (**11**) identical with the product obtained[12] by similar treatment of the mixed anomers **9** and **10**, while β alloside **10** underwent similar conversion into the corresponding 6-bromo 4-benzoate **12**, obtained, however, in substantially lower yield as an amorphous, levorotatory product.

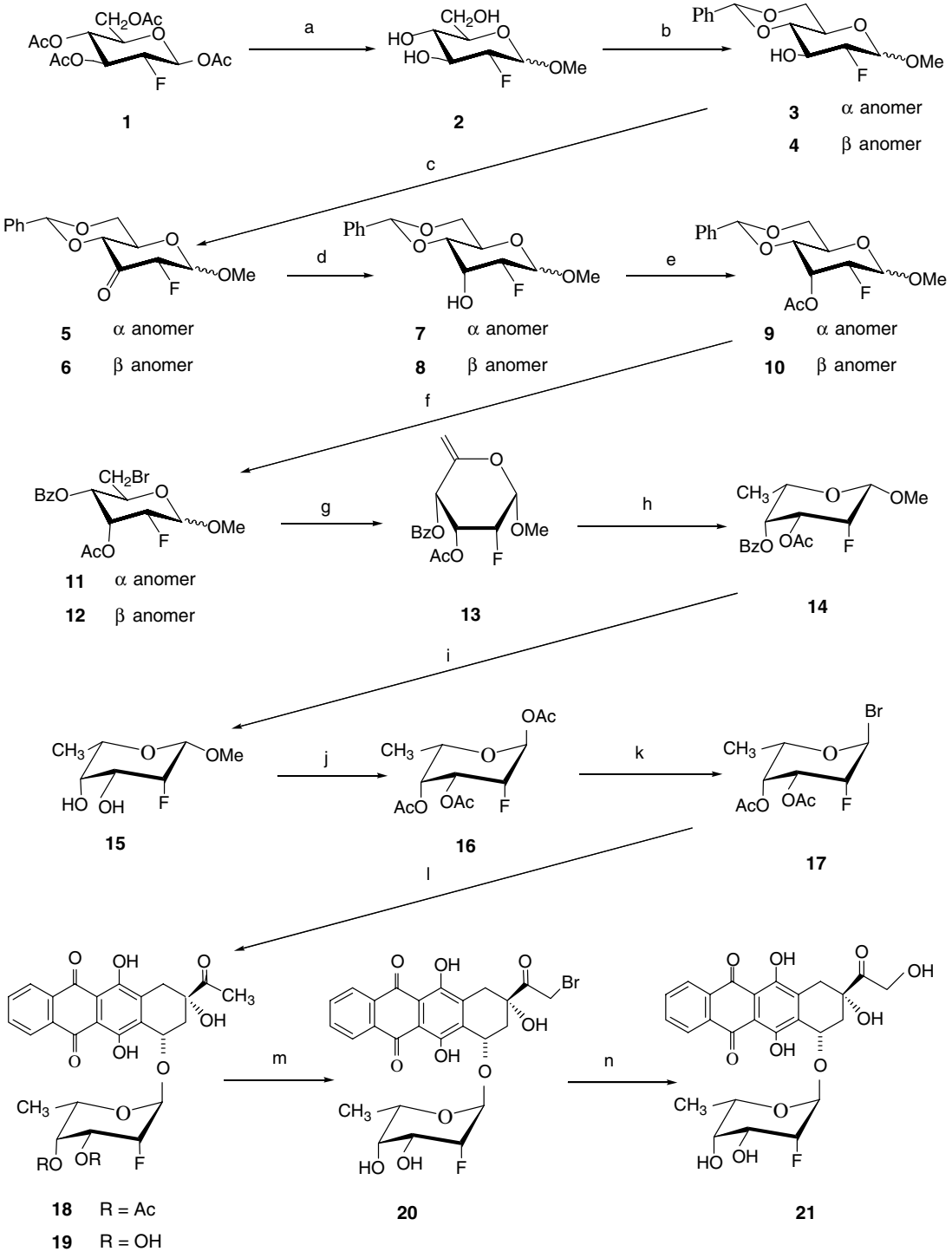
Dehydrobromination of the pure α 6-bromo compound **11** by the action of 1,8-diaza-7-bicyclo-[5.4.0]undecene (DBU) in boiling benzene led in 93% yield to 5-enopyranoside **13**, obtained as a low-melting, dextrorotatory solid having physical constants concordant with those earlier reported.[18] Hydrogenation of **13** over palladium–barium sulfate proceeded stereospecifically by 'topside' attack on the face of the ring opposite to the other four ring substituents to effect net conversion of the D-sugar precursor to the L-sugar product, methyl 3-*O*-acetyl-4-*O*-benzoyl-2-fluoro-β-L-talopyranoside (**14**), previously[18] described as an oil and now obtained crystalline in 88% yield. Catalytic transesterification of **14** then afforded methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside[18] (**15**), which was subjected to acid-catalyzed acetolysis, yielding 89% of crystalline 1,3,4-tetra-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose (**16**), along with a minor proportion of its apparent anomer. The α-anomeric configuration of **16**, anticipated from consideration of the anomeric effect, was supported by its strong levorotation and from NMR data; in particular, the very small (~1 Hz) $J_{1,2}$ coupling constant, indicative of the diequatorial orientation of H-1 and H-2.

Compound **16**, the glycon precursor for the anthracycline glycosides reported here, was earlier prepared by Tsuchiya and co-workers[13] by a sequence starting from L-fucose, but the present approach, based on the general strategy of our synthesis[20] of daunosamine from D-mannose, has the advantage of a high net yield from the inexpensive sugar precursor D-mannose.

Triacetate **16** was converted by the action of titanium tetrabromide into the corresponding glycosyl bromide **17**, obtained as an oil in 82% yield, and allowed to react without delay with (+)-(7*S*,9*S*)-4-demethoxydaunomycinone (idarubicinone)[17,21] in dichloromethane solution in the presence of mercuric bromide, yellow mercuric oxide, and molecular sieves. Chromatographic resolution of the product mixture afforded orange crystals of the acetylated target glycoside, 4-demethoxy-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**18**), in 47% yield, and whose detailed ^{1}H, ^{13}C, and ^{19}F NMR data supported the assigned structure and α anomeric configuration ($J_{1,2}$ 1.2 Hz).

O-Deacetylation of **18** was effected with dilute aqueous sodium hydroxide at 0 °C to give a 78% yield of crystalline 4-demethoxy-(7-*O*-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**19**). Monobromination of **19** at the 14-position was performed in methanol–1,4-dioxane solution at 0 °C by careful addition of a small excess of bromine in chloroform solution and TLC monitoring. The resultant 14-bromo derivative **20**, obtained in 52% yield, was finally transformed into the 14-hydroxy analogue, 4-demethoxy-(7-*O*-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (**21**), by reaction with warm aqueous dimethyl sulfoxide and TLC monitoring, followed by preparative TLC. The anthracycline glycosides **18**–**21** were all characterized by high-resolution mass spectrometry together with 500-MHz ^{1}H NMR, along with ^{13}C and ^{19}F NMR data. The patent literature[12,22] cites the final target, compound **21**; CAS Registry No. 125555-22-8.

The four anthracycline glycosides **18**–**21** were evaluated in vitro, along with adriamycin, for antitumor activity against five human-tumor cell-lines, including lung, colon, and breast carcinoma, melanoma, and



Scheme 1. Reagents: (a) MeOH, H^+; (b) $PhCH(OMe)_2$, TsOH; (c) pyridinium dichromate; (d) $NaBH_4$; (e) Ac_2O, DMAP; (f) NBS; (g) DBU; (h) Pd, H_2; (i) NaOMe; (j) Ac_2O, H_2SO_4; (k) $TiBr_4$; (l) demethoxydaunomycinone, Hg salts; (m) Br_2; (n) Me_2SO, H_2O.

Glioblastoma multiforme CNS tumor. All showed activity, and details will be reported elsewhere. It is noteworthy that computational studies on DNA binding[23] suggest that removal of the 4-methoxy group from the aglycon of anthracycline antibiotics correlates with increase in antitumor potency and selectivity.

3. Experimental

3.1. General methods

Melting points were determined in open glass capillaries with a Thomas–Hoover apparatus and are uncorrected.

Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AM-250, AM-300, or AM-500 spectrometers, and chemical shifts refer to an internal standard of Me_4Si ($\delta = 0.00$). ^{19}F spectra were recorded at 235 MHz with a Bruker AM-250 instrument. Assignments were supported for all compounds by ^{1}H–^{1}H COSY experiments before and after D_2O exchange as well as by ^{1}H–^{13}C HETCOR, and also by ^{19}F decoupled spectra for compounds **18**, **19**, and **20**. TLC was performed on precoated glass plates (0.25 mm) of Silica Gel 60 F-254 (E. Merck); components were detected by spraying the plates with 10% H_2SO_4 and subsequent heating. Column chromatography was performed with Silica Gel 60 (230–400 mesh, E. Merck). Solvents were dried and redistilled just prior to use. Mass spectra (FAB) were recorded at The Ohio State University Chemical Instrument Center with Kratos MS-30 and VG-70 250S mass spectrometers; peak intensities are recorded as percent of the base peak. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrophotometer. Elemental analyses were determined by Atlantic Microlab, Inc., Norcross Atlanta, Georgia.

3.2. Methyl 2-deoxy-2-fluoro-α,β-D-glucopyranoside (2)

Prepared as described earlier[18] by acid-catalyzed methanolysis of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose and obtained as an oil in 95% yield.

3.3. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α- and β-D-glucopyranosides (3 and 4)

α,α-Dimethoxytoluene (2.78 mL, 18.5 mmol) and *p*-toluenesulfonic acid (26 mg) were added to a suspension of the anomeric mixture **2** (2.27 g, 11.6 mmol) in dry MeCN (50 mL), and the mixture was stirred under argon at room temperature, as previously described.[18] After 3 h, TLC (1:1 hexane–EtOAc) showed the disappearance of **2** and a double spot for the products. The solvent was removed at 40 °C to yield a light-yellow oil, which was dissolved in boiling ether and the resulting solution cooled to −20 °C. This gave a white solid, which by TLC and NMR was an anomeric mixture (40% α, 60% β), yield 2.96 g (90%). This was subjected to flash chromatography with hexane–EtOAc with increasing proportions of EtOAc. The first few fractions gave methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**4**), which was crystallized from hexane–EtOAc; yield 1.20 g, mp 184–186 °C, $[\alpha]_D^{20}$ −53.3 (*c* 1.1, $CHCl_3$); MS: *m*/*z* 285 (100, M+1), 253 (2.7, M+1−MeOH), 207 (2.9, $M^+-C_6H_5$), 179 (4.4, M+1−C_6H_5CHO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.35 (m, 5H, aryl), 5.53 (s, 1H, H-benzylidene), 4.51 (dd, 1H, $J_{1,2}$ 7.5, $J_{1,F}$ 3.8 Hz, H-1), 4.37 (dd, 1H, $J_{6e,6a}$ 10.3, $J_{5,6e}$ 4.9 Hz, H-6e), 4.25 (dt, 1H, $J_{2,F}$ 50.03, $J_{2,3}$ 8.5 Hz, H-2), 4.00 (dt, 1H, $J_{3,F}$ 15.4, $J_{3,4}$ 9.2 Hz, H-3), 3.77 (t, 1H, $J_{5,6a}$ 9.4 Hz, H-6a), 3.59 (s, 3H, OCH_3), 3.53 (t, 1H, $J_{4,5}$ 9.4 Hz, H-4), 3.45 (dt, 1H, $J_{5,6e}$ 4.9 Hz, H-5), 2.70 (d, 1H, $J_{3,OH}$ 2.7 Hz, OH, D_2O exchangeable); ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 136.71, 129.37, 128.36, 126.23 (Ar–C), 101.93 (benzylidene-C), 101.89 ($J_{1,F}$ 23.71 Hz, C-1), 92.55 ($J_{2,F}$ 186.55 Hz, C-2), 79.93 ($J_{4,F}$ 8.99 Hz, C-4), 72.31 ($J_{3,F}$ 19.62 Hz, C-3), 68.48 (C-6), 66.03 (C-5), 57.40 (C–OMe); ^{19}F NMR δ −201.459 (ddd). Anal. Calcd for $C_{14}H_{17}FO_5$ (284.30): C, 59.14; H, 6.04. Found: C, 58.30, H, 5.98.

3.4. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-glucopyranoside (3)

This product was obtained by flash chromatography of the anomeric mixture and was crystallized from ether; yield 0.80 g, mp 156–157 °C, $[\alpha]_D^{20}$ +105.3 (*c* 0.7, $CHCl_3$); (lit.[24] mp 163–164 °C, $[\alpha]_D^{20}$ +116.3 ($CHCl_3$)).

3.5. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-D-*ribo*-hexopyranosid-3-ulose (5 and 6)

To a suspension of the mixture of **3** and **4** (3.32 g, 11.67 mmol) in dry CH_2Cl_2 (150 mL) was added pyridinium dichromate (7.90 g, 20.19 mmol), pyridinium trifluoroacetate (0.90 g, 4.67 mmol), and crushed 3Å molecular sieves (11.68 g, dried overnight at 160 °C in vacuo). After 4 h, TLC (2:1 hexane–EtOAc) indicated no starting material. The mixture was diluted with ether (250 mL) and filtered through a sintered-glass funnel containing a small pad of silica gel with 10% $MgSO_4$. Evaporation of the solvent gave the product as a white solid; yield 3.30 g (96%), which by TLC and NMR was an anomeric mixture. Analytical samples of the α and β glycosiduloses were obtained by flash chromatography with 1:1 hexane–EtOAc.

3.6. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-*ribo*-hexopyranosid-3-ulose (5)

Compound **5** had a mp of 209–210 °C (with decomposition), $[\alpha]_D^{20}$ +122.6 (*c* 0.47, $CHCl_3$), [lit.[18] mp 216–217 °C, $[\alpha]_D^{20}$ +114 (*c* 1, $CHCl_3$)]; ν_{max} 1752 cm^{-1} (CO); MS: *m*/*z* 283 (73, M+1), 251 (3, M+1−MeOH), 205 (3, $M^+-C_6H_5$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.48 (m, 2H, aryl), 7.38–7.34 (m, 3H, Ar), 5.55 (s, 1H, H-benzylidene), 5.31 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 5.02 (ddd, 1H, $J_{2,F}$ 47.0, $J_{2,4}$ 1.3 Hz, H-2), 4.42 (dd, 1H, $J_{6e,6a}$ 10.1, $J_{5,6e}$ 4.5 Hz, H-6e), 4.24 (dd, 1H, $J_{4,5}$ 9.7, $J_{4,F}$ 0.95 Hz, H-4), 4.11 (dt, 1H, $J_{5,6a}$ 10.0 Hz, H-5), 3.92 (t, 1H, H-6a), 3.50 (s, 3H, OCH_3); ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 192.42 (d, $J_{3,F}$ 16.1 Hz, C-3), 136.12, 129.44, 128.32, 126.39 (Ar–C), 102.1 (benzylidene-C), 101.03 (d, $J_{1,F}$ 19.59 Hz, C-1), 88.6 (d, $J_{2,F}$ 207.32 Hz,

C-2), 81.7 (C-4), 69.31 (C-6), 65.14 (C-5), 55.91 (C–OMe); ^{19}F NMR: δ −208.069 (d). Anal. Calcd for $C_{14}H_{15}FO_5$ (282.28): C, 59.56; H, 5.37, Found: C, 59.34; H, 5.31.

3.7. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-*ribo*-hexopyranosid-3-ulose (6)

This compound had a mp of 225–230 °C (with decomposition), $[\alpha]_D^{20}$ −53.5 (*c* 0.6, $CHCl_3$); ν_{max} 1742 cm^{-1} (CO); MS: 283 (34, M+1), 205 (5.1, $M^+-C_6H_5$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.48 (m, 2H, Ar), 7.39–7.34 (m, 3H, Ar), 5.57 (s, 1H, Ph–CH), 4.79 (ddd, 1H, $J_{2,F}$ 47.05, $J_{1,2}$ 7.5, $J_{2,4}$ 1.56 Hz, H-2), 4.67 (dd, 1H, $J_{1,F}$ 5.1 Hz, H-1), 4.52 (dd, 1H, $J_{6e,6a}$ 10.45, $J_{5,6e}$ 4.9 Hz, H-6e), 4.30 (dd, 1H, $J_{4,5}$ 9.9, $J_{4,F}$ 1.09 Hz, H-4), 3.91 (t, 1H, $J_{5,6a}$ 9.9 Hz, H-6a), 3.63 (dt, 1H, H-5), 3.65 (s, 3H, OCH_3); ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 192.71 (d, $J_{3,F}$ 16.3 Hz, C-3), 135.98, 129.51, 128.37, 126.34 (Ar–C), 104.16 (d, $J_{1,F}$ 24.1 Hz, C-1), 101.97 (benzylidene-C), 91.75 (d, $J_{2,F}$ 201.7 Hz, C-2), 81.56 (C-4), 69.04 (C-6), 66.68 (C-5), 57.88 (C–OMe); ^{19}F NMR: δ −208.164 (dd). Anal. Calcd for $C_{14}H_{15}FO_5$ (282.28): C, 59.56; H, 5.37, Found: C, 59.50; H, 5.29.

3.8. Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α- and β-D-allopyranoside (7 and 8)

A solution of **5** and **6** (0.90 g, 3.17 mmol) in EtOH (50 mL) was cooled to −20 °C and $NaBH_4$ (0.362 g, 9.57 mmol) was added. It was stirred at this temperature for 1 h and then allowed to warm slowly to room temperature, at which point it became homogeneous. The excess of $NaBH_4$ was decomposed by dropwise addition of 1.0 M HOAc until effervescence ceased. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with satd aq $NaHCO_3$ followed by brine. The organic layer was dried ($MgSO_4$), and the solvent removed to give an oily foam; yield 0.750 g (83.3%), which by TLC (1:1 hexane–EtOAc) was a mixture of two products. The product was chromatographed over silica gel (80 g, using 10% EtOAc in hexane initially and gradually increasing the percentage of EtOAc to 20%, 25%, 30%, and 35%). The less-polar product **8** came at 35% EtOAc–hexane; yield 0.280 g (37%). It was crystallized from EtOAc and hexane as granules, mp 192–194 °C. NMR confirmed it to be methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-allopyranoside (**8**); $[\alpha]_D^{20}$ −43.4 (*c* 1.4, $CHCl_3$); MS: *m*/*z* 285 (60, M+1), 253 (7.5, M+1−MeOH), 207 (4, $M^+-C_6H_5$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.51–7.35 (m, 5H, Ar), 5.55 (s, 1H, H-benzylidene), 4.88 (dd, 1H, $J_{1,2}$ 7.79, $J_{1,F}$ 2.27 Hz, H-1), 4.53 (dt, $J_{3,F}$ 7.48, $J_{2,3}$ 2.7, $J_{3,4}$ 2.5 Hz, H-3), 4.42 (dd, 1H, $J_{6e,6a}$ 10.3, $J_{5,6e}$ 5.0 Hz, H-6e), 4.26 (ddd, 1H, $J_{2,F}$ 46.3, $J_{1,2}$ 7.79, $J_{2,3}$ 2.7 Hz, H-2), 4.04 (dt, 1H, $J_{4,5}$ 9.6, $J_{5,6a}$ 10.3 Hz, H-5), 3.74 (t, 1H, H-6a), 3.59 (s, 3H, OCH_3), 3.55 (dd, 1H, H-4); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ 136.79, 129.37, 128.39, 126.20 (Ar–C), 101.99 (benzylidene-C), 99.71 (d, $J_{1,F}$ 24.15 Hz, C-1), 89.06 (d, $J_{2,F}$ 190.63 Hz, C-2), 78.04 (d, $J_{4,F}$ 6.35 Hz, C-4), 69.0 (C-6), 68.11 (d, $J_{3,4}$ 17.36 Hz, C-3), 62.99 (C-5), 57.46 (C–OMe); ^{19}F NMR: δ −204.37 (dd). Anal. Calcd for $C_{14}H_{17}FO_5$ (284.30): C, 59.14; H, 6.04. Found: C, 59.17; H, 6.05.

The more-polar product **7** was eluted with 40% EtOAc–hexane; yield 0.462 g (62%). It was crystallized from EtOAc and hexane as needles; mp 116 °C. ^{1}H NMR confirmed it to be methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-allopyranoside (**7**), $[\alpha]_D^{20}$ +129.3 (*c* 1.29, $CHCl_3$) (lit.[18] mp 109–110 °C, $[\alpha]_D$ +126 ($CHCl_3$)); MS: *m*/*z*: 285 (100, M+1), 253 (31, M+1−MeOH), 207 (5.2, $M^+-C_6H_5$), 179 (5.9, M+1−C_6H_5CHO); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.53–7.34 (m, 5H, Ar), 5.56 (s, 1H, H-benzylidene), 4.95 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.51 (dt, $J_{2,F}$ 45.28, $J_{2,3}$ 3.4 Hz, H-2), 4.51 (br m, 1H, H-3), 4.39 (dd, 1H, $J_{6e,6a}$ 10.3, $J_{5,6e}$ 5.0 Hz, H-6e), 4.15 (dt, 1H, $J_{5,6a}$ 10.0, $J_{4,5}$ 9.9 Hz, H-5), 3.74 (t, 1H, H-6a), 3.5 (s, 3H, OCH_3), 3.48 (br d, 1H, H-4), 3.12 (d, 1H, *J* 7.14 Hz, OH, D_2O exchangeable); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ 136.98, 129.21, 128.28, 126.30 (Ar–C), 102.09 (benzylidene-C), 98.40 (d, $J_{1,F}$ 22.32 Hz, C-1), 85.49 (d, $J_{2,F}$ 195.48 Hz, C-2), 78.07 (d, $J_{4,F}$ 7.17 Hz, C-4), 69.00 (C-6), 68.38 (d, $J_{3,F}$ 18.11 Hz, C-3), 57.69 (C-5), 56.28 (C–OMe); ^{19}F NMR: δ −202.98 (dd). Anal. Calcd for $C_{14}H_{17}FO_5$ (284.30): C, 59.14; H, 6.04. Found: C, 59.24; H, 6.08.

3.9. Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-allopyranoside (9)

To a solution of **7** (0.46 g, 1.61 mmol) in dry pyridine (15 mL) at 0 °C were added Ac_2O (5 mL) and a catalytic amount of 4-dimethylaminopyridine, and the solution was kept overnight under stirring and warming to room temperature. Removal of the solvent using toluene (4 × 20 mL) for azeotropic distillation of pyridine gave a yellow oil, which was purified by column chromatography over silica gel using 3:2 hexane–EtOAc. It was crystallized from isopropyl ether; yield 0.50 g (98%), mp 79–80 °C, $[\alpha]_D^{20}$ +93.9 (*c* 0.59, $CHCl_3$) (lit.[12] mp 79–80 °C, $[\alpha]_D$ +91); MS: *m*/*z* 327 (82, M+1), 295 (77, M+1−MeOH), 267 (2.6, M+1−AcOH), 221 (23, M+1−C_6H_5CHO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.43 (m, 5H, Ar), 5.91 (m, 1H, H-3), 5.53 (s, 1H, H-benzylidene), 4.91 (d, 1H, $J_{1,2}$ 4.3 Hz, H-1), 4.62 (dt, 1H, $J_{2,F}$ 43.4, $J_{2,3}$ 4.1 Hz, H-2), 4.35 (dd, 1H, $J_{6e,6a}$ 10.4, $J_{5,6e}$ 5.14 Hz, H-6e), 4.19 (dt, 1H, $J_{5,6a}$ 10.1, $J_{4,5}$ 9.9 Hz, H-5), 3.71 (t, 1H, H-6a), 3.62 (ddd, 1H, $J_{3,4}$ 2.74, $J_{4,F}$ 1.53 Hz, H-4), 3.49 (s, 3H, OCH_3); ^{13}C

NMR (75.469 Hz, $CDCl_3$): δ 170.30 (O*C*OCH$_3$), 136.80, 128.98, 128.12, 125.93 (Ar–C), 101.37 (benzylidene-C), 97.35 (d, $J_{1,F}$ 21.50 Hz, C-1), 84.26 (d, $J_{2,F}$ 198.78 Hz, C-2), 75.74 (d, $J_{4,F}$ 5.81 Hz, C-4), 68.94 (C-6), 66.56 (d, $J_{3,F}$ 17.35 Hz, C-3), 57.94 (C–OMe), 55.99 (C-5), 20.86 (OCO*C*H$_3$); ^{19}F NMR: δ −202.66 (dd). Anal. Calcd for $C_{16}H_{19}FO_6$ (326.34): C, 58.88; H, 5.88. Found: C, 58.77; H, 5.83.

3.10. Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-allopyranoside (10)

To a solution of **8** (63 mg, 0.22 mmol) in dry pyridine (2 mL) at 0 °C were added Ac_2O (1 mL) and a catalytic amount of 4-dimethylaminopyridine, and the solution was left overnight under stirring to warm to room temperature. Removal of the solvent using toluene (3 × 5 mL) for azeotropic distillation of pyridine gave a yellow oil, which was purified by column chromatography over silica gel using 3:2 hexane–EtOAc and crystallized from hexane–EtOAc; yield 70 mg (98%). mp 169–170 °C; $[\alpha]_D^{20}$ −59 (*c* 0.6, $CHCl_3$); MS: *m*/*z* 327 (91.5, M+1), 295 (47, M+1−MeOH), 267 (4.3, M+1−CH_3CO_2H), 221 (19, M+1−C_6H_5CHO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.26 (m, 5H, Ar), 5.85 (m, 1H, H-3), 5.45 (s, 1H, H-benzylidene), 4.72 (dd, 1H, $J_{1,2}$ 7.84, $J_{1,F}$ 2.04 Hz, H-1), 4.30 (ddd, 1H, $J_{2,F}$ 45.80, $J_{2,3}$ 3.36, $J_{2,4}$ 0.9 Hz, H-2), 4.32 (dd, 1H, $J_{6e,6a}$ 10.2, $J_{5,6e}$ 4.9 Hz, H-6e). 3,85 (dt, 1H, $J_{5,6a}$ 9.5, $J_{4,5}$ 9.4 Hz, H-5), 3.67 (t, 1H, H-6a), 3.57 (dd, 1H, $J_{3,4}$ 1.1 Hz, H-4), 3.53 (s, 3H, OCH$_3$); ^{13}C NMR (76.469 MHz, $CDCl_3$):δ 169.36 (–O*C*OCH$_3$), 136.66, 129.00, 128.13, 125.89 (Ar–C), 101.38 (benzylidene-C), 100.10 (d, $J_{1,F}$ 24.22 Hz, C-1), 87.02 (d, $J_{2,F}$ 194.12 Hz, C-2), 76.25 (d, $J_{4,F}$ 5.66 Hz, C-4), 68.85 (C-6), 67.82 (d, $J_{3,F}$ 17.74 Hz, C-3), 63.99 (s, C–OMe), 57.22 (C-5), 20.67 (OCO*C*H$_3$); ^{19}F NMR: δ −203.94 (br dd). Anal. Calcd for $C_{16}H_{19}FO_6$ (326.34): C, 58.88; H, 5.88. Found: C, 58.79; H, 5.83.

3.11. Methyl 3-*O*-acetyl-4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-allopyranoside (11)

Dry CCl_4 (100 mL) was filtered over alumina into a round-bottomed flask containing a mixture of **9** (1.57 g, 4.8 mmol) and *N*-bromosuccinimide (NBS, 0.96 g, 5.38 mmol). The NBS and $BaCO_3$ had been dried in vacuo for 3 h at 80 °C. The resulting mixture was stirred vigorously at 75–80 °C under reflux. The color changed to yellow, yellow red, yellow, and then colorless. TLC (3:2 hexane–EtOAc) showed the reaction to be complete after 2 h. The mixture was filtered through Celite and the filter cake was washed with hot CCl_4. The solvent was removed and the residue was dissolved in CH_2Cl_2 (150 mL). The resulting solution was washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvent removed to yield a light-yellow solid. This solid was recrystallized from 95% EtOH to yield **11** (1.70 g, 88%), mp 149 °C, $[\alpha]_D^{20}$ +104 (*c* 1, $CHCl_3$) (lit.[18] mp 149–150 °C, $[\alpha]_D$ +105); MS: *m*/*z* 405 (22, M^+), 373 (52, M−MeOH), 325 (3, M−HBr); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.96–7.41 (m, 5H, Ar), 5.95 (m, 1H, H-3), 5.09 (ddd, 1H, $J_{4,5}$ 9.6, $J_{3,4}$ 3.1, $J_{4,F}$ 1.45 Hz, H-4), 5.00 (d, 1H, $J_{1,2}$ 4.04 Hz, H-1), 4.70 (dt, 1H, $J_{2,F}$ 40.0, $J_{2,3}$ 4.02 Hz, H-2), 4.45 (ddd, 1H, $J_{5,6a}$ 7.0, $J_{5,6b}$ 2.4 Hz, H-5), 3.60 (dd, 1H, $J_{6a,6b}$ 11.2, H-6b), 3.47 (dd, 1H, H-6a), 2.12 (s, 3H, OAc); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ 170.08, 164.64 (–O*C*OPh, –O*C*OCH$_3$), 133.66, 129.64, 128.86, 128.57 (Ar–C), 97.06 (d, $J_{1,F}$ 21.69 Hz, C-1), 83.72 (d, $J_{2,F}$ 198.94 Hz, C-2), 68.59 (d, $J_{4,F}$ 5.15 Hz, C-4), 66.78 (d, $J_{3,F}$ 17.61 Hz, C-3), 64.97 (C-5), 56.30 (C–OMe), 31.67 (C-6), 20.75 (OCO*C*H$_3$); ^{19}F NMR δ −203.57 (dd). Anal. Calcd for $C_{16}H_{18}BrFO_6$ (405.23): C, 47.42; H, 4.49. Found: C, 47.35, H, 4.48.

3.12. Methyl-3-*O*-acetyl-4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-allopyranoside (12)

Dry CCl_4 (5 mL) was filtered over alumina into a round-bottomed flask containing a mixture of **10** (39 mg, 0.12 mmol), *N*-bromosuccinimide (0.031 g, 0.17 mmol), and $BaCO_3$ (35 mg, 0.17 mmol). The NBS and $BaCO_3$ had been dried in vacuo for 3 h at 80 °C. The resulting mixture was stirred vigorously at 75–80 °C under reflux until the usual color changes were complete (2 h). TLC (3:2 hexane–EtOAc) indicated no significant change in the polarity of the product and the starting material. Addition of more NBS and $BaCO_3$ did not bring any further color changes. The mixture was filtered through Celite and the filter cake was washed with hot CCl_4. The solvent was removed and the residue dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvent removed. It was then subjected to column chromatography. Product **12** was obtained as an amorphous residue; yield 15 mg (31%), $[\alpha]_D^{20}$ −84.0 (*c* 0.1, $CHCl_3$); MS: *m*/*z* 405 (17, M^+), 373 (17, M−MeOH), 325 (2, M−HBr); ^{1}H NMR (250MHz, $CDCl_3$): δ 7.96–7.42 (m, 5H, Ar), 5.96 (dt, 1H, $J_{3,F}$ 8.4, $J_{3,4}$ 3.1, $J_{2,3}$ 3.2 Hz, H-3), 5.08 (ddd, 1H, $J_{4,5}$ 9.7, $J_{4,F}$ 1.3 Hz, H-4), 4.88 (dd, 1H, $J_{1,2}$ 7.6, $J_{1,F}$ 1.8 Hz, H-1), 4.46 (ddd, 1H, $J_{2,F}$ 46.4 Hz, H-2), 4,20 (ddd, 1H, $J_{5,6a}$ 7.0, $J_{5,6b}$ 2.6 Hz, H-5), 3.64 (s, 3H, OCH$_3$), 3.59 (dd, 1H, $J_{6a,6b}$ 11.2 Hz, H-6b), 3.46 (dd, 1H, H-6a), 2.14 (s, 3H, OAc); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ 169.29, 164.78 (–O*C*OPh, –O*C*OCH$_3$), 133.72, 129.68, 128.80, 128.60 (Ar–C), 99.53 (d, $J_{1,F}$ 24.09 Hz, C-1), 86.25 (d, $J_{2,F}$ 195.29 Hz, C-2), 71.85 (C-5), 69.31 (d, $J_{4,F}$ 4.46 Hz, C-4), 67.87 (d, $J_{3,F}$ 17.29 Hz, C-3), 57.07 (C–OMe), 31.26 (C-6), 20.59 (OCO*C*H$_3$); ^{19}F NMR: δ −203.93 (br dd).

3.13. Methyl 3-*O*-acetyl-4-*O*-benzoyl-2,6-dideoxy-2-fluoro-α-D-*ribo*-hex-5-enopyranoside (13)

A solution of **11** (1.01 g, 2.49 mmol) in dry benzene (50 mL) was heated to reflux and DBU (1.13 mL, 7.55 mmol) was added to the solution under argon. TLC (3:1 hexane–EtOAc) after 3 h indicated the disappearance of starting material. The mixture was diluted with benzene, washed with 5% HCl (2 × 50 mL), satd aq $NaHCO_3$ (2 × 50 mL), and brine, dried (Na_2SO_4), and the solvent removed in vacuo to yield **13** (0.75 g, 93%), as a chromatographically homogeneous, very low-melting solid; $[\alpha]_D^{20}$ +91 (*c* 1, $CHCl_3$) (lit.[18] $[\alpha]_D$ +91); MS: *m*/*z* 325 (M+1), 293 (M+1−MeOH), 265 (M+1−HOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.08–7.40 (m, 5H, Ar), 5.76 (d, 1H, $J_{3,4}$ 3.7 Hz, H-4), 5.47 (dt, 1H, $J_{3,F}$ 19.83, $J_{2,3}$ 3.4 Hz, H-3), 4.97 (br s, 1H, H-6a), 4.88 (br s, 1H, H-6b), 4.83 (dt, 1H, $J_{2,F}$ 47.99 Hz, H-2), 4.81 (dd, 1H, $J_{1,F}$ 9.70, $J_{1,2}$ 2.3 Hz, H-1), 3.65 (s, 3H, OCH_3), 2.09 (s, 3H, OAc); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ 170.09, 169.18 (–O*C*OPh, –O*C*OCH_3), 149.49 (C-5), 133.37, 129.31, 128.42 (Ar–C), 101.82 (C-6), 99.72 (d, $J_{1,F}$ 18.23 Hz, C-1), 84.51 (d, $J_{2,F}$ 197.3 Hz, C-2), 67.59 (d, $J_{3,F}$ 16.47 Hz, C-3), 66.78 (d, $J_{4,F}$ 2.74 Hz, C-4), 57.18 (C–OMe), 20.67 (OCO*C*H_3); ^{19}F NMR: δ −212.9 (ddd). Anal. Calcd for $C_{16}H_{17}FO_6$ (324.32): C, 59.25; H, 5.29. Found: C, 59.18; H, 5.33.

3.14. Methyl 3-*O*-acetyl-4-*O*-benzoyl-2,6-dideoxy-2-fluoro-β-L-talopyranoside (14)

To a solution of **13** (0.643 g, 1.98 mmol) in dry EtOAc (10 mL) was added 10% Pd/$BaSO_4$ (0.090 g), and hydrogen was gently bubbled into the stirred mixture. TLC (2:1 hexane–EtOAc) after 30 min showed the consumption of starting material. The mixture was filtered through Celite, the filter cake washed with EtOAc and the filtrate evaporated. The residue was purified by column chromatography over silica gel using 10% EtOAc in hexane initially and gradually increasing the percentage of EtOAc. Product **14** (0.57 g, 88%) was obtained as very low-melting flakes, mp 49 °C, $[\alpha]_D^{20}$ −128 (*c* 1.9, $CHCl_3$) (the previously reported value[18] may have been in error); MS: *m*/*z* 327 (69, M+1), 307 (7.8, M+1−HF), 295 (79, M+1−MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.16–7.40 (m, 5H, Ar), 5.42 (dd, 1H, $J_{3,4}$ 3.6, $J_{4,5}$ 1.0 Hz, H-4), 5.04 (dt, 1H, $J_{3,F}$ 31.7, $J_{2,3}$ 2.7 Hz, H-3), 4.74 (dd, 1H, $J_{2,F}$ 51.4 Hz, H-2), 4.47 (d, 1H, $J_{1,F}$ 18.4 Hz, H-1), 3.87 (dq, 1H, $J_{5,6}$ 6.4 Hz, H-5), 3.64 (s, 3H, OCH_3), 2.02 (s, 3H, OAc), 1.32 (d, 3H, H-6); ^{13}C NMR (62.896 Hz, $CDCl_3$): δ 169.98, 166.38 (O*C*OPh, O*C*OCH_3), 133.20, 130.15, 129.39, 128.34 (Ar–C), 99.97 (d, $J_{1,F}$ 15.61 Hz, C-1), 85.63 (d, $J_{2,F}$ 195.31 Hz, C-2), 70.16 (C-4), 69.15 (d, $J_{3,F}$ 15.80 Hz, C-3), 68.32 (C-5), 57.43 (C–OMe), 20.55 (OCO*C*H_3), 16.04 (C-6). Anal. Calcd for $C_{16}H_{19}FO_6$ (326.34): C, 58.88; H, 5.88, Found: C, 58.81; H, 5.87.

3.15. Methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside (15)

Prepared from **14** essentially as described,[18] compound **15** was obtained as a white solid, mp136–137 °C; $[\alpha]_D^{20}$ +63.7 (*c* 1.45, $CHCl_3$); MS: *m*/*z* 181 (15.4, M+1), 149 (66.4, M+1−MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.71 (d, 1H, $J_{2,F}$ 51.05 Hz, H-2), 4.31 (d, $J_{1,F}$ 20.12 Hz, H-1), 3.54–3.59 (m, 6H, OCH_3, H-3, H-4, H-5), 3.0 (br, 1H, OH), 1.93 (br, 1H, OH), 1.40 (d, 1H, $J_{5,6}$ 6.46 Hz, H-6); ^{13}C NMR (62.896 Hz, $CDCl_3$); δ 100.52 (d, $J_{1,F}$ 20.12 Hz, C-1), 90.28 (d, $J_{2,F}$ 182.90 Hz, C-2), 71.575, 71.278 (C-4, C-5), 69.28 (d, $J_{3,F}$ 16.10 Hz, C-3), 57.32 (C–OMe), 16.163 (C-6); ^{19}F NMR: δ −220.7. Anal. Calcd for $C_7H_{13}FO_4$ (180.19): C, 46.66; H, 7.29, Found: C, 46.77; H, 7.29.

3.16. 1,3,4-Tri-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose (16)

To a solution of methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside (**15**, 0.190 g,1.05 mmol) in dry $MeNO_2$ (6 mL) were added Ac_2O (1.10 mL) and H_2SO_4 (30 μL), and the solution was stirred at room temperature. After 4 h, TLC (3:1 hexane–acetone) showed the consumption of all of the starting material and the presence of two less-polar spots. Addition of more H_2SO_4 did not change the composition of the products. The solution was made neutral with satd aq $NaHCO_3$ and the mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$), and the solvent evaporated to a syrup that was purified by flash chromatography with hexane–acetone, using gradient elution. The less-polar product (**16**) crystallized from ether–hexane; yield 0.272 g (89%), mp 102–103 °C, $[\alpha]_D^{20}$ −109 (*c* 1, $CHCl_3$), (lit.[13] mp 102–103 °C, $[\alpha]_D^{20}$ −111). The ^{1}H NMR spectral data were identical with those reported.[7] MS: *m*/*z* 293 (5.2, M+1), 233 (100, M+1−CH_3CO_2H), 173 (5.6, M+1−2CH_3CO_2H), 113 (3, M+1−3CH_3CO_2H). Anal. Calcd for $C_{12}H_{17}FO_7$ (292.28): C, 49.32; H, 5.86. Found C 49.24; H, 5.82.

3.17. 3,4-Di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl bromide (17)

To a solution of **16** (0.200 g, 0.684 mmol) in dry EtOAc–CH_2Cl_2 (12 mL) was added $TiBr_4$ (0.81 g, 2.2 mmol), and the resulting mixture was stirred at room temperature. After 48 h, the mixture was diluted with MeCN (8 mL), and anhydrous NaOAc (1.05 g) was added. The resulting mixture was stirred until the color faded to pale yellow. After filtration, the solvent was removed to yield a pale-yellow oil, which was purified by column

chromatography (hexane–acetone) using gradient elution to give the product as a colorless oil, yield 0.175 g (82%). The ^{1}H NMR spectral data of the product were identical with those reported.[13]

3.18. 4-Demethoxy-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (18)

A mixture of (+)-(7*S*,9*S*)-4-demethoxydaunomycinone[17] (0.206 g, 0.56 mmol), freshly dried yellow HgO (0.61 g, 2.8 mmol), $HgBr_2$ (0.183 g, 0.5 mmol), and freshly activated 3 Å crushed molecular sieves (2.0 g) in dry CH_2Cl_2 (10 mL) was stirred for 30 min under argon at room temperature. A solution of **17** (0.160 g, 0.5 mmol) in dry CH_2Cl_2 (3 mL) was added slowly and the mixture was stirred in the dark for 24 h. TLC in 4:1 benzene–acetone indicated the disappearance of starting materials and the formation of a product slightly less polar than 4-demethoxydaunomycinone, but more polar than **17**. The mixture was diluted with $CHCl_3$, filtered, and the organic solution washed successively with 30% aq KI, satd aq $NaHCO_3$, and then dried ($MgSO_4$), and evaporated. The orange residue was purified by column chromatography over silica gel with benzene–acetone. The amorphous product crystallized from $CHCl_3$–hexane as orange crystals, mp 168–169 °C, yield 0.076 g (47%), $[\alpha]_D^{20}$ +104 (*c* 0.2, $CHCl_3$); ν_{max}^{KBr}: 1744, 1721, 1626, 1588 cm^{-1}; MS: *m*/*z* 601.15 (4, M+1), 600.14 (6, M$^+$), 583.22 (1.3, M−OH), 557.22 (0.45, M−CH_3CO), 522.57 (0.6, M−OH−CH_3CO_2H), 367.97 (7.8, aglycon), 350.92 (18, M+1−glycon), 333.01 (36, M+1−glycon−H_2O), 306.99 (52, M−glycon−$COCH_3$), 291.00 (100.0, M+1−glycon−H_2O−CH_2=C=O), 233.06 (28.8, M+1−aglycon); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.59 (s, 1H, enolic OH), 13.29 (s, 1H, enolic OH), 8.35 (m, 2H, Ar–H), 7.86 (m, 2H, Ar–H), 5.63 (dd, 1H, $J_{1',F}$ 8.31, $J_{1',2'}$ 1.2 Hz, H-1′), 5.30 (dd, 1H, $J_{7,8a}$ 4.5, $J_{7,8e}$ <1 Hz, H-7), 5.24 (dd, 1H, $J_{3',4'}$ 3.4, $J_{4',5'}$ <1 Hz, H-4′), 5.017 (dt, 1H, $J_{3',F}$ 32.70, $J_{2',3'}$ 3.1 Hz, H-3′), 4.60 (br d, 1H, $J_{2',F}$ 49.32 Hz, H-2′), 4.37 (dq, 1H, $J_{5',6'}$ 6.6 Hz, H-5′), 3.85 (s, 1H, D_2O exchangeable, 9-OH), 3.25 (dd, 1H, $J_{10e,10a}$ 18.9, $J_{8e,10e}$ 1.7 Hz, H-10e), 2.98 (d, 1H, H-10a), 2.41 (s, 3H, H-14), 2.36 (br d, 1H, $J_{8e,8a}$ 15.5 Hz, H-8e), 2.20 (dd, 1H, H-8a), 2.17 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.27 (d, 3H, H-6′); ^{13}C NMR (125.759 Hz, $CDCl_3$): δ 211.19 (C-13), 186.96 (C-5 or C-12), 186.74 (C-5 or C-12), 170.89 (O*C*OCH$_3$), 169.70 (O*C*OCH$_3$), 156.46 (C-6 or C-11), 156.14 (C-6 or C-11), 135.79 (C-12a), 134.67, 134.63 (C-6a, C-10a), 133.44, 133.35 (C-2, C-4), 132.53 (C-4a), 127.17, 127.08 (C-1, C-3), 111.78, 110.99 (C-5a, C-11a), 101.28 (d, $J_{1',F}$ 31.73 Hz, C-1′), 85.01 (d, $J_{2',F}$ 184.2 Hz, C-2′), 76.26 (C-9), 71.22 (C-7), 68.78 (C-4′), 66.58 (d, $J_{3',F}$ 15.4 Hz, C-3′), 66.082 (C-5′), 35.28 (C-8), 33.36 (C-10), 24.63 (C-14), 20.73, 20.611 (OCO*C*H$_3$), 16.15 (C-6′); ^{19}F NMR (235.36 MHz), δ −201.593 (ddd, *J* 9.64, 32.71, 42.36 Hz). HREIMS: 600.1644 for $C_{30}H_{29}FO_{12}$, Calcd 600.1643. Anal. Calcd for $C_{30}H_{29}FO_{12}\cdot 0.5H_2O$ (609.58): C, 59.11; H, 4.97. Found: C, 59.22; H, 5.04.

3.19. 4-Demethoxy-7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (19)

Compound **18** (60 mg, 0.09 mmol) was taken up in 0.2 M aq NaOH (5 mL) and stirred at 0 °C. The solution turned deep purple. The progress of the reaction was monitored by TLC (4:1 benzene–acetone). After 5 h the reaction was complete, showing the formation of a very polar product, R_f 0.1. The mixture was carefully neutralized with cold aqueous M HCl, whereupon the color changed to orange. The solution was extracted with $CHCl_3$ and washed with satd aq NaCl. The organic layer was dried ($MgSO_4$), evaporated, and the residue crystallized from $CHCl_3$ and hexane; mp 185–187 °C, yield 40 mg (78%); $[\alpha]_D^{20}$ +47.1 (*c* 0.14, $CHCl_3$); ν_{max}: 1716, 1626, 1588 cm^{-1} (KBr); MS: *m*/*z* 517.35 (3, M+1), 516.34 (4.8, M$^+$), 368 (7.2, aglycon), 351 (16, M+1−glycon), 333 (17, M+1−glycon−H_2O), 307 (29, M−glycon−CH_3CO), 291 (44, M+1−glycon−H_2O−CH_2=C=O), 149 (82, M+1−aglycon); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.60 (s, 1H, enolic OH), 13.28 (s, 1H, enolic OH), 8.36 (m, 1H, Ar–H), 7.86 (m, 1H, Ar–H), 7.70 (m, 1H, Ar–H), 7.53 (m, 1H, Ar–H), 5.59 (dd, 1H, $J_{1',F}$ 9.35, $J_{1',2'}$ <1 Hz, H-1′), 5.27 (dd, 1H, $J_{7,8a}$ 4.4, $J_{7,8e}$ <1 Hz, H-7), 4.63 (br d, 1H, $J_{2',F}$ 49.0, $J_{2',3'}$ 2.8 Hz, H-2′), 4.21 (br q, 1H, $J_{5',6'}$ 6.5, $J_{4',5'}$ 1.4 Hz, H-5′), 3.96 (s, 1H, D_2O exchangeable, 9-OH), 3.66 (br m, 1H, H-4′), 3.65 (dt, 1H, $J_{3',F}$ 32.43, $J_{3',4'}$ 2.8 Hz, H-3′), 3.25 (dd, 1H, $J_{10a,10e}$ 19.1, $J_{8e,10e}$ 1.75 Hz, H-10e), 2.97 (d, 1H, H-10a), 2.96 (s, 1H, D_2O exchangeable, 3′ or 4′ OH), 2.41 (s, 3H, H-14), 2.37 (br d, $J_{8e,8a}$ 14.9 Hz, H-8e), 2.19 (dd, 1H, H-8a), 1.94 (dd, 1H, D_2O exchangeable, *J* 11.3, 8.1 Hz, 3′ or 4′ OH), 1.38 (d, 3H, H-6′); ^{13}C NMR (125.759 Hz, $CDCl_3$): δ 211.10 (C-13), 186.91 (C-5 or C-12), 186.65 (C-5 or C-12), 156.41 (C-6 or C-11), 156.09 (C-6 or C-11), 135.70, 133.38, 133.28, 132.60 (C-4a, C-6a, C-10a, C-12a), 134.66, 130.85, 128.79, 127.10 (C-1, C-2, C-3, C-4), 111.73, 110.93 (C-5a, C-11a), 101.03 (d, $J_{1',F}$ 31.87 Hz, C-1′), 89.3 (d, $J_{2',F}$ 172.30 Hz, C-2′), 76.34 (C-9), 71.05 (C-7), 68.17 (C-4′),67.71 (C-5′), 66.13 (d, $J_{3',F}$ 15.61 Hz, C-3′), 35.20 (C-8), 33.34 (C-10), 24.57 (C-14), 16.33 (C-6′); ^{19}F NMR: (235.36 MHz), δ −201.688 (m). HREIMS: *m*/*z* 516.145 for $C_{26}H_{25}FO_{10}$. Calcd 516.143.

3.20. 14-Bromo-4-demethoxy-7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone (20)

To a solution of **19** (20 mg, 0.036 mmol) in a mixture of dry MeOH (0.5 mL) and 1,4-dioxane (1.6 mL) was

added a solution of Br_2 in $CHCl_3$ (0.4 mL, prepared from 10.0 g of bromine in 100 mL of $CHCl_3$). The solution was stirred at 0–5 °C for 4 h and then kept at room temperature. The progress of the reaction was monitored by TLC, which indicated complete consumption of starting material after 6 days and the formation of a slightly less-polar product. The reaction was terminated by first removing the excess of Br_2 by bubbling air through the mixture followed by precipitating the product (**20**) with ether (10 mL). It was collected by centrifugation and washed twice with ether (2 mL); yield 12 mg (50%), mp 202 °C, $[\alpha]_D^{20}$ +171 (*c* 0.14, 1:1 $CHCl_3$–MeOH); MS: *m*/*z* 596.27 (1.3, M+1), 595.30 (0.7, M^+), 447.15 (0.3, aglycon), 430.13 (1.3, M+1−glycon), 429.12 (1.7, aglycon−H_2O), 149.05 (69, M+1−aglycon); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.62 (s, 1H, enolic OH), 13.26 (s, 1H, enolic OH), 8.36 (m, 2H, Ar–H), 7.85 (m, 2H, Ar–H), 5.64 (dd, 1H, $J_{1',F}$ 9.61, $J_{1',2'}$ <1 Hz, H-1′), 5.33 (br m, 1H, H-7), 4.62 (br d, 1H, $J_{2',F}$ 48.12 Hz, H-2′), 4.57 (d, 1H, $J_{14a,14b}$ 13.1 Hz, H-14 a or b), 4.32 (d, 1H, H-14 a or b), 4.17 (q, 1H, $J_{5',6'}$ 6.6, $J_{4',5'}$ <1 Hz, H-5′), 4.10 (s, 1H, D_2O exchangeable, 9-OH), 3.68 (br m, 1H, H-4′), 3.63 (br dt, 1H, $J_{3',F}$ 33, $J_{2',3'}$ 3.2, $J_{3',4'}$ 3.7 Hz, H-3′), 3.34 (dd, 1H, $J_{10e,10a}$ 19.0, $J_{8e,10e}$ 1.5 Hz, H-10e), 3.04 (d, 1H, H-10a), 2.89 (d, 1H, D_2O exchangeable, *J* 10.9 Hz, 3′-OH), 2.52 (br d, 1H, $J_{8e,8a}$ 15.0 Hz, H-8e), 2.32 (dd, 1H, $J_{7,8a}$ 4.15 Hz, H-8a), 1.88 (dd, 1H, D_2O exchangeable, *J* 11.6, 8.1 Hz, 4′-OH), 1.39 (d, 1H, H-6′); ^{13}C NMR (125.759 Hz, $CDCl_3$): δ 204.87 (C-13), 187.05 (C-5 or C-12), 186.85 (C-5 or C-12), 155.75 (C-6 or C-11), 155.59 (C-6 or C-11), 134.89, 133.43, 133.34, 131.89 (C-4a, C-6a, C-10a, C-12a), 134.80, 134.75, 127.21, 127.17 (C-1, C-2, C-3, C-4), 112.03, 111.21 (C-5a, C-11a), 100.98 (d, $J_{1',F}$ 32.15 Hz, C-1′), 89.13 (d, $J_{2',F}$ 172.05 Hz, C-2′), 76.77 (C-9), 71.72 (C-4′), 70.96 (C-7), 68.02 (C-5′), 65.99 (d, $J_{3',F}$ 16.16 Hz, C-3′), 36.46 (C-8), 34.50 (C-10), 31.09 (C-14), 16.48 (C-6′); ^{19}F NMR (235.36 MHz), δ −201.496 (m).

3.21. 4-Demethoxy-7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (21)

A solution of **20** (10 mg, 0.017 mmol) in Me_2SO (0.6 mL) and water (0.2 mL) was stirred at 80 °C under nitrogen. The reaction was monitored by TLC, which after 3 h indicated the disappearance of **20** and the formation of a polar product. The product was isolated by the removal of Me_2SO under vacuum. The residue was dissolved in 1:1 $CHCl_3$–MeOH and the product was precipitated by the addition of isopropyl ether, and collected by centrifugation. The amorphous residue was purified by preparative TLC on RP-18 plates (4:13:3 acetonitrile–MeOH–water); yield 6 mg (67%), mp 192 °C, $[\alpha]_D^{20}$ +259 (*c* 0.1, 1:1 $CHCl_3$–MeOH); FABMS: *m*/*z* 532.20 (0.06, M^+), 384.10 (0.2, aglycon), 366.12 (0.1, aglycon−H_2O), 353.10 (0.2, aglycon−CH_2OH), 348.07 (0.25, aglycon−$2H_2O$), 335.12 (0.1, aglycon−H_2O−CH_2OH), 166.11 (0.8, glycon). HREIMS: *m*/*z* 531.967 (M^+) for $C_{26}H_{25}FO_{11}$. Calcd 532.138; 366.0730 for $C_{20}H_{14}O_7$ (aglycon−H_2O), calcd 366.0739; 348.0636 for $C_{20}H_{12}O_6$ (aglycon−$2H_2O$), calcd 348.0634; ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.64 (s, 1H, enolic OH), 13.28 (s, 1H, enolic OH), 8.37 (m, 2H, Ar–H), 7.87 (m, 2H, Ar–H), 5.63 (br d, 1H, $J_{1',F}$ 9.21, $J_{1',2'}$ <1 Hz, H-1′), 5.36 (br m, 1H, H-7), 4.75 (br s, 2H, H-14), 4.62 (br d, 1H, $J_{2',F}$ 49.0 <1 Hz, H-2′), 4.12 (br q, 1H, H-5′), 3.98 (s, 1H, D_2O exchangeable, 9-OH), 3.67 (br m, 1H, H-4′), 3.61 (dt, 1H, $J_{3',F}$ 31.80 Hz, H-3′), 3.33 (dd, 1H, $J_{10e,10a}$ 19.0, $J_{8e,10e}$ 1.8 Hz, H-10e), 3.07 (d, 1H, H-10a), 2.96-2.40 (br m, 2H, D_2O exchangeable, 14-OH, 3′-OH), 2.42 (br d, 1H, $J_{8e,8a}$ 14.9 Hz, H-8e), 2.25 (dd, 1H, $J_{7,8a}$ 4.24 Hz, H-8a), 1.88 (br m, 1H, D_2O exchangeable, 4′-OH), 1.40 (d, 3H, $J_{5',6'}$ 6.5 Hz, H-6′); ^{19}F NMR (235.36 MHz), δ −201.561 (m). Insufficient sample was available for ^{1}H–^{13}C HETCOR.

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