# Synthesis and biological activity of (*R*)-2′-fluorocarminomycin

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Methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-talopyranoside was hydrolyzed to the free sugar, (*R*)-2-fluorodaunosamine hydrochloride, which was converted into the α-1,4-di-*O*-acetyl-*N*-trifluoroacetyl derivative. The latter was condensed with carminomycinone by use of trimethylsilyl triflate as the activating agent, and the product was deprotected to give the title compound. Cytotoxicity of the new fluoroanthracycline against a number of tumor cell lines in vitro equalled that of parent carminomycin, and activities of the two compounds against P-388 murine leukemia in vivo were the same, although the fluoro derivative was fourfold less potent and appeared to be somewhat less toxic.

*Key words*: (*R*)-2-fluorodaunosamine hydrochloride, synthesis; (*R*)-2′-fluorocarminomycin, synthesis and biological activity.

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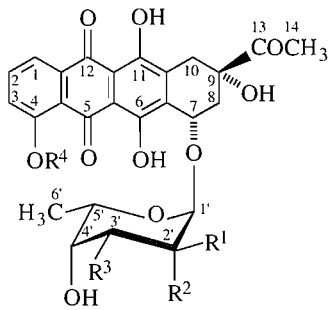
On a hydrolysé le méthyl-3-amino-2,3,6-tridésoxy-2-fluoro-β-L-talopyranoside en sucre libre, le chlorhydrate de la (*R*)-2-fluorodaunosamine, que l'on a transformé en dérivé α-1,4-di-*O*-acétyl-*N*-trifluoroacétyle. On a condensé ce dernier avec la carminomycinone à l'aide de triflate de triméthylsilyle comme agent activateur et on a déprotégé le produit pour obtenir le composé mentionné dans le titre. Les effets cytotoxiques in vitro de cette nouvelle fluoroanthracycline contre de nombreuses lignes de cellules tumorales sont équivalents à ceux de la carminomycine naturelle. Par ailleurs, l'activité antitumorale in vivo des deux composés contre la leucémie murine P-388 demeure la même quoique le dérivé fluoro s'est avéré quatre fois moins puissant et est apparu comme étant quelque moins toxique.

*Mots clés* : synthèse du chlorhydrate de la (*R*)-2-fluorodaunosamine, synthèse et activité biologique de la (*R*)-2′-fluorocarminomycine.

## Introduction

In our first article (1) from a program concerned with the synthesis of anthracycline antitumor agents fluorinated in the sugar moiety, a rationale was provided for attempts to procure derivatives bearing a fluorine atom at the position C-2′, and the question of a possible effect of stereochemistry at that position was discussed. Prior and concurrent work by Horton *et al.* (2) has shown that certain structural modifications of daunorubicin (**1***a*), substituted at C-2′ by iodine, bromine, or chlorine, exhibited significantly enhanced antitumor activity and decreased toxicity, but only when the halo atom was axially oriented (**1***b* and 4′-epimers; *R*-2′ configuration); the nature of the halogen atom appeared to have little influence on activity, but *S*-2′ epimers **1***c* (equatorial halogen) were inactive (2). Although Horton *et al.* had previously demonstrated (3) that the 3′-amino group in anthracyclines is not essential for antitumor activity, as was confirmed by the properties of the 3′-deamino-3′-hydroxy (or acetoxy) derivatives **1***b*, we targeted 3′-amino-2′-fluoro glycosides in the hope of gaining further insights into the factors that govern drug efficacy and toxicity.

Our first efforts in that direction (1, 4) had produced (*S*)-2′-fluorodaunorubicin (**2**), also synthesized by Lukacs and co-workers (5), which proved active against a variety of tumor cell lines in vitro and against L1210 murine leukemia in vivo but showed a somewhat lower potency as compared with parent **1***a*. Compound **2** was nontoxic at the highest dose level tested (4), contrary to **1***a*, and it was intriguing to observe retention of activity (albeit diminished) in a derivative bearing an *equatorial* 2′-halo substituent. This raised expectations that an analog having an axial 2′-fluoro substituent might be a superior drug, and we set out first to prepare (*R*)-2-fluoro-L-daunosamine, in the form of its methyl β-pyranoside (6), as the sugar component



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **1***a* | H | H | $NH_2$ | Me |
| **1***b* | H | I, Br, or Cl | OH or OAc | Me |
| **1***c* | I, Br, or Cl | H | OH or OAc | Me |
| **1***d* | H | F | OH | Me |
| **2** | F | H | $NH_2$ | Me |
| **3** | H | H | $NH_2$ | H |
| **4** | H | F | $NH_2$ | H |

required for synthesis of such an analog. While that work was in progress, the Umezawas and co-workers (7) published a study highly relevant to this topic, namely, the synthesis of 3′-deamino-(*R*)-2′-fluoro-3′-hydroxydaunorubicin (**1***d*) and its 14-hydroxy derivative (i.e., the corresponding adriamycin analog); strong antitumor activity and low toxicity were displayed by both of these compounds, especially so by the latter. We now record the synthesis of (*R*)-2′-fluorocarminomycin (**4**) and the results of biological testing in comparison with parent carminomycin (**3**). The latter drug has been stated (8) to be more potent than **1***a*, from which it differs structurally solely by its lack of the 4-methyl ether group (9).

## Results and discussion

The synthesis of **4** proceeded essentially in analogy to that of **2** (4), except for the step of aglycon glycosylation. Thus, methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-talopyranoside (**5**) (6) was hydrolyzed with 4 M hydrochloric acid to give the free amino

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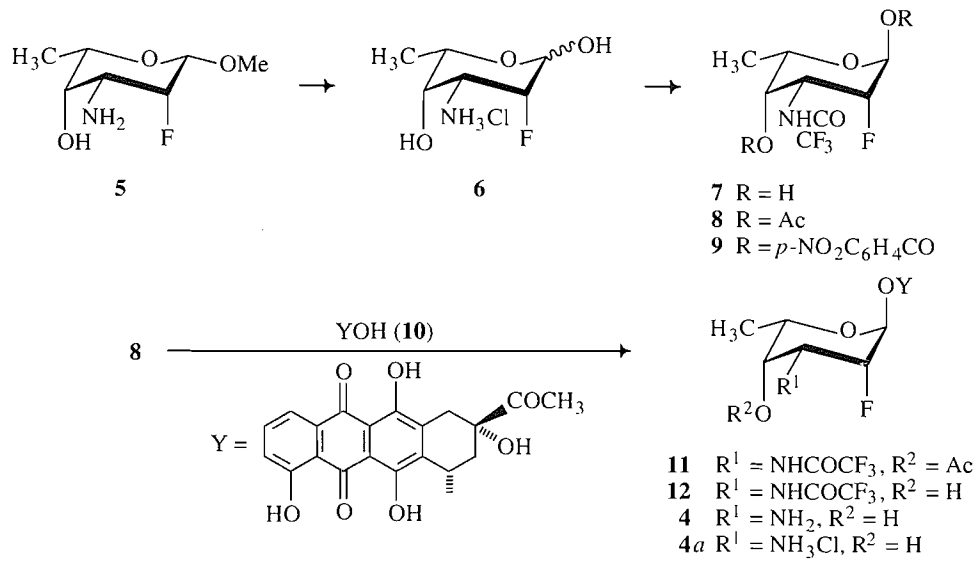


sugar hydrochloride **6**, obtained as a crystalline, anomeric mixture. The sugar was sequentially *N*-trifluoroacetylated and *O*-acetylated under the general conditions of daunosamine acylation (10), affording the acyl derivatives **7** and **8** isolated crystalline as pure α-anomers. (By contrast, their (*S*)-2 epimers had been obtained (4) as anomeric mixtures.) The yields of **6–8** were 88–91%.

Compound **8** was condensed with carminomycinone (**10**) by use of trimethylsilyl triflate as the activating agent, according to the method employed by Terashima and co-workers (11) for a synthesis of 4-demethoxydaunorubicin. The 4′-*O*-acetyl-*N*-trifluoroacetyl anthracycline **11** was isolated crystalline in 51% yield; since 33% of unchanged **8** was recovered, the yield based on sugar actually consumed in the reaction was 75%.[3] Sodium methoxide-catalyzed *O*-deacetylation of **11** gave (*R*)-2′-fluoro-*N*-trifluoroacetylcarminomycin (**12**), characterized by tlc only, which was directly *N*-deprotected by treatment with aqueous barium hydroxide, to furnish a 82% overall yield of the target compound **4**, analytically characterized both as the free base and as its hydrochloride **4***a*.

The $^1$H nmr data for the new compounds (see the Experimental) were in full accord with the depicted structures, and it may be noted in particular that the magnitudes of all observed $^1$H–$^{19}$F coupling constants conformed well with expectations based on previous, detailed discussions (1, 6). Mention of a few salient points may suffice. Thus, the vicinal coupling between the fluorine atom and the anomeric proton ($^3J_{H\text{-}1,F\text{-}2}$) in **7–9**, **11**, and **4** was 8.3 ± 0.3 Hz (9.7 Hz in **4***a*), which provided unambiguous proof for an H-1*eq*,F-2*ax gauche* relationship and, hence, the α-anomeric configuration. The $^3J_{H\text{-}1,F\text{-}2}$ value empirically calculated (1, 6, 12) for a 2-deoxy-2-fluorohexopyranose having a 1*ax*,2*ax*,3*eq* substituent arrangement is 6 Hz. By contrast, $^3J_{H,F}$ values for vicinal, *trans*-diaxial nuclei are usually in the range of 19–34 Hz, depending on electronegativity of substituents present (13); examples are $^3J_{H\text{-}1,F\text{-}2}$ = 20.5 Hz for **5** (6) and 22 Hz for **6**-β, and $^3J_{F\text{-}2,H\text{-}3}$ = 33–34 Hz for **5** (6), **7–9**, and **11**. (The $^3J_{F\text{-}2,H\text{-}3}$ values for **4**, **4***a*, and **6**-α should fall in the same range, but they could not be determined.) The geminal coupling constants $^2J_{H\text{-}2,F\text{-}2}$ of **4**, **4***a*, **6**-α, **7–9**, and **11** were all in the range of 48–49.3 Hz, whereas that of **6**-β was 51 Hz, in agreement with empirically calculated (1, 6, 12) values of 48 and 51 Hz, respectively.

Further confirmation of the α-anomeric configuration of the glycoside **11** and its precursors **7** and **8** was derived from their $^{13}$C nmr spectra, which displayed C-1 signals (for **11**, read C-1′ etc.) as doublets with $^2J_{C\text{-}1,F\text{-}2}$ = 30.4 ± 1 Hz, C-3 signals as doublets with $^2J_{F\text{-}2,C\text{-}3}$ = 16.0 ± 0.4 Hz, and C-4 signals as singlets ($^3J_{F\text{-}2,C\text{-}4}$ = 0 Hz). The magnitude of $^2J_{C\text{-}1,F\text{-}2}$ indicated an *anti* orientation of the anomeric oxygen atom with respect to the fluorine atom; the $^2J_{F\text{-}2,C\text{-}3}$ values were as expected for structures wherein the coupled C-atom does not bear an electronegative substituent *anti* to the F-atom, and zero vicinal coupling $^3J_{F\text{-}2,C\text{-}4}$ was in line with the *gauche* F-2—C-4 arrangement (6, 13, 14). Finally, the nmr parameters for **4**, **11**, and **8** were in excellent harmony with those reported (7) for **1***d*, its 3′,4′-diacetate, and their progenitor 1,3,4-tri-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose.

*Biological activity*

Tests to compare antitumor activity of the fluorocarminomycin **4***a* with that of parent carminomycin (**3**) hydrochloride were performed by Bristol–Myers Company, Wallingford, Connecticut. Both compounds showed equally high potencies in vitro, in cytotoxicity tests against five human ovarian and colon cancer cell lines (A2780DDP, A2780S, HCT-116, HCT/VM46, and HCT/VP35), with IC-50 values ranging from <0.001 to 0.03 μg/mL. Tests in vivo against murine P-388 lymphocytic leukemia showed **4** and **3** to be equally active, achieving median survival time increases (T/C values) of ~200%, although **3** was about fourfold more potent in terms of effective dose levels (Table 1). Acute toxicity appeared to be lower in **4**, as judged from a slower onset of weight loss at higher doses, but no toxic deaths occurred within 5 days after treatment with either drug at the dose levels tested.

[3]For condensation of 1,4-di-*O*-acetyl-*N*-trifluoroacetyldaunosamine with 4-demethoxydaunorubicin, followed by 4′-*O*-deacetylation of the product, Terashima and co-workers (11) reported a 70% yield. By use of the corresponding 1,4-bis-*p*-nitrobenzoate, the condensation was almost quantitative and the 4′-*O*-deprotected product was elaborated in 83% yield (11). We encountered initial difficulties in attempting to prepare the 1,4-bis-*p*-nitrobenzoate (**9**) of **7**, and although this ester was eventually obtained (for $^1$H nmr data, see the section for **8** in the Experimental), its full characterization and (possibly advantageous) use for glycosylation of **10** were dispensed with, the goal of the project having meanwhile been attained.

TABLE 1. Antitumor activity in vivo of carminomycin and (*R*)-2′-fluorocarminomycin against murine P-388 lymphocytic leukemia[a]

| Compound (hydrochloride) | Dose (mg/kg)[b] | MST[c] (days) | T/C[d] (%) | AWC[e] (g) |
|---|---|---|---|---|
| **3** | 1.2 | 12 | 133 | −0.9 |
| | 0.6 | 19 | 211 | −0.8 |
| | 0.3 | 15.5 | 172 | 0.6 |
| | 0.15 | 13 | 144 | 0.0 |
| **4** | 2.4 | 18 | 200 | −0.5 |
| | 1.2 | 16.5 | 183 | −0.1 |
| | 0.6 | 12.5 | 139 | 0.4 |
| | 0.3 | 12 | 133 | 0.3 |
| | 0.15 | 11 | 122 | 0.2 |
| Control | | 9 | 100 | 0.8 |

[a]In $CDF_1$ mice (six per test) inoculated i.p. with $10^6$ P-388 cells on day 0.
[b]Single dose administered i.p. on day 1.
[c]Median survival time.
[d]Ratio of MST of treated mice to that of untreated controls.
[e]Average weight change recorded on day 4.

## Experimental

General preparative and instrumental methods were the same as those previously employed (1, 4, 6). The following solvent combinations (v/v) were used for thin-layer chromatography (tlc) and column chromatography on silica gel: methanol–chloroform, 1:3 (A) and 1:6 (B); methanol–acetone, 1:1 (C); and ethyl acetate – hexanes, 1:1 (D) and 1:2 (E). Optical rotations were measured at ~25°C. Infrared data ($\nu_{max}$) obtained for all new compounds were consistent with the structures, and only a few especially significant bands are listed. Mass-spectral data (*m/z*) were obtained in the chemical ionization mode, using ether as the ionizing gas. The $^1H$ nmr spectra were recorded at 300 MHz from solutions in deuteriochloroform, unless otherwise indicated.

*3-Amino-2,3,6-trideoxy-2-fluoro-α,β-L-talose hydrochloride (6)*

A solution of amino glycoside **5** (6) (385 mg) in 4 M hydrochloric acid (40 mL) was boiled under reflux for 6 h, after which time the hydrolysis was complete (tlc, solvent A). The acid was evaporated under diminished pressure with repeated additions of water, and the remaining aqueous solution of the product was treated with activated charcoal and concentrated, to give a greenish solid that was thoroughly dried over KOH *in vacuo*. Trituration with hot acetone then removed the colored impurity and gave **6** as a crystalline monohydrate (415 mg, 88%), mp 201°C; $[\alpha]_D$ −35° (*c* 1, $H_2O$); $^1H$ nmr (DMSO-$d_6$ + $D_2O$) δ: 5.14 (dd, ~0.6H, $J_{1,2} \approx 1.5$, $J_{1,F} = 8$ Hz, H-1α), 4.69 (d, ~0.4H, $J_{1,F} = 22$ Hz, H-1β), 4.57 (dnm, ~0.4H, $J_{2,F} \approx 51$ Hz, H-2β), 4.51 (dnm, ~0.6H, $J_{2,F} = 49.3$ Hz, H-2α), 4.07 (q, ~0.6H, $J_{5,6} = 6.4$ Hz ($J_{4,5} < 1$ Hz), H-5α), 3.5-region (m, H-3,4,5β), 1.18 and 1.14 (2 d, total intensity 3H, $J = 6.4$ Hz, *C*-Me); *m/z*: 166 (100%, $M^+ + 1 -$ HCl), 148 (47%, $M^+ + 1 -$ HCl − $H_2O$). Anal. calcd. for $C_6H_{13}ClFNO_3 \cdot H_2O$ (219.6): C 32.81, H 6.88, N 6.38; found: C 32.65, H 6.88, N 6.33.

*2,3,6-Trideoxy-2-fluoro-3-trifluoroacetamido-α-L-talopyranose (7)*

Trifluoroacetic anhydride (2.45 mL) in dry ether (10 mL) was added dropwise at 0°C to a magnetically stirred suspension of **6** (350 mg) in dry ether (20 mL). Cooling was discontinued after 45 min and the solution kept at room temperature for 2.5 h, after which time tlc (solvent A) revealed the complete conversion of **6** ($R_f$ 0.15) into a single, new product ($R_f$ 0.5). The excess of reagent was removed by coevaporation with several added portions of ether. To reverse *O*-acylation, a solution of the residue in dry methanol (30 mL) was first rendered slightly alkaline (pH ~ 8) with methanolic 0.5 M $NaOCH_3$ and, after 1 h, the pH was adjusted to 7 with a few drops of acetic acid in methanol. Concentration of the mixture followed by column chromatography (solvent D) afforded **7** (410 mg, 91%), mp 134–135°C; $[\alpha]_D$ −51° (*c* 1, $Me_2CO$); $\nu_{max}^{KBr}$: 3400, 1715, 1530 $cm^{-1}$; $^1H$ nmr (acetone-$d_6$) δ: 8.06 (br, exchangeable, NH), 6.01 (dd, exchangeable, $J_{OH,F} = 2.5$, $J_{1,OH} = 4.5$ Hz, OH-1), 5.29 (ddd (dd after $D_2O$ exchange), $J_{1,2} = 1.7$, $J_{1,F} = 8.6$ Hz, H-1), 4.57 (d of septets, $J_{2,F} = 49.3$, $J_{2,4} = 1.2$, $J_{1,2} = 1.8$, $J_{2,3} = 3$ Hz, H-2), 4.43 (dt (t after $D_2O$ exchange), 0.5H, $J_{2,3} = J_{3,4} = 3$, $J_{3,NH} = 8.3$ Hz, downfield part of ddt for H-3, with upfield part coinciding with the H-5 signal; $J_{3,F} \approx 33$ Hz), 4.32 (qd, $J_{4,5} = 1.6$, $J_{5,6} = 6.6$ Hz, H-5), 3.63 (d, ($J_{4,OH} \approx 10$ Hz) of nm with $W \approx 6$ Hz; nm after $D_2O$ exchange, H-4), 3.26 (dd, exchangeable, $J_{F,OH} = 3.9$, $J_{4,OH} = 9.9$ Hz, OH-4), 1.21 (d, 3H, $J = 6.6$ Hz, *C*-Me). Upon the addition of $D_2O$ to the sample solution (to produce the exchange phenomena just listed), the spectrum showed a set of additional (weak) signals, attributable to the β-anomer arising by anomerization; $^{13}C$ nmr (50.29 MHz, acetone-$d_6$) δ: 157.7 (q, $^2J_{F,C} = 38$ Hz, $CF_3CO$), 116.7 (q, $^1J_{F,C} \approx 290$ Hz, $CF_3$), 92.4 (d, $^2J_{1,F} = 30.4$ Hz, C-1), 88.7 (d, $^1J_{2,F} = 175.7$ Hz, C-2), 69.7 (s, C-4), 66.7 (s, C-5), 49.1 (d, $^2J_{F,C} = 15.6$ Hz, C-3), 16.8 (s, C-6); *m/z*: 262 (53%, $M^+ + 1$), 244 (100%, $M^+ + 1 - H_2O$). Anal. calcd. for $C_8H_{11}F_4NO_4$ (261.2): C 36.79, H 4.25, F 29.10, N 5.36; found: C 36.90, H 4.47, F 29.26, N 5.38.

*1,4-Di-O-acetyl-2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-α-L-talopyranose (8)*

Compound **7** (457 mg) was treated for 15 min at −17°C with acetic anhydride (12 mL) containing 1 drop of concentrated $H_2SO_4$. Complete conversion of the slow-moving **7** into a single product ($R_f$ 0.55) was indicated by tlc (solvent D). The mixture was stirred with ice water and aqueous $NaHCO_3$ to decompose the excess of anhydride, and the product was extracted into $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$), and evaporated, and the solid residue was chromatographed on a column of $SiO_2$ (solvent E), to give colorless **8** (548 mg, 91%), mp 148–149°C (recrystallized from ether–hexane); $[\alpha]_D$ −110.3° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$: 3330 and 3260 (NH), 1750, 1550 $cm^{-1}$; $^1H$ nmr δ: 6.72 (d, $J_{3,NH} \approx 8.5$ Hz, NH), 6.32 (dd, $J_{1,2} = 1.7$, $J_{1,F} = 8.4$ Hz, H-1), 5.175 (nm, $W_H = 7$ Hz, H-4), 4.57 (ddt, $J_{2,3} = J_{3,4} = 3.5$, $J_{3,NH} = 8.7$, $J_{3,F} = 33.5$ Hz, H-3), 4.51 (d of nm, $J_{2,F} = 48$ Hz, H-2), 4.20 (qd, $J_{4,5} \approx 1$, $J_{5,6} = 6.5$ Hz, H-5), 2.18 and 2.14 (2 s, 3H each, 2 OAc), 1.19 (d, 3H, $J = 6.5$ Hz, *C*-Me); $^{13}C$ nmr (50.29 MHz, $CDCl_3$) δ: 171.0 and 168.4 (2 s, 2 *Me*CO), 157.0 (q, $^2J_{C,F} = 38.4$ Hz, $CF_3CO$), 115.4 (d, $^1J_{C,F} = 288.3$ Hz, $CF_3$), 90.1 (d, $^2J_{1,F} = 32.4$ Hz, C-1), 84.2 (d, $^1J_{2,F} = 182.6$ Hz, C-2), 68.1 and 67.2 (2 s, C-4,5), 46.25 (d, $^2J_{3,F} = 16.4$ Hz, C-3), 20.5 and 20.1 (2 s, 2 *CO*Me), 16.1 (s, C-6). *m/z*: 346 (1%, $M^+ + 1$), 286 (100%, $M^+ + 1 -$ AcOH). Anal. calcd. for $C_{12}H_{15}F_4NO_6$ (345.2): C 41.74, H 4.38, F 22.01; found: C 41.93, H 4.48, F 21.79.

The analogous *1,4-di-O-p-nitrobenzoate* **9**, obtained as a pale yellow solid from **7** by treatment with *p*-nitrobenzoyl chloride and pyridine, showed the following $^1H$ nmr data: δ: 8.35–8.20 (m, 8H, arom.), 6.81 (d, $J_{3,NH} = 7.8$ Hz, NH), 6.69 (dd, $J_{1,2} = 1.5$, $J_{1,F} = 8.5$ Hz, H-1), 5.56 (m, $W_H = 6.5$ Hz, H-4), 4.80 (ddt, $J_{2,3} \approx J_{3,4} \approx 3.5$, $J_{3,NH} = 8$, $J_{3,F} = 33$ Hz, H-3), 4.78 (d of nm, $J_{2,F} \approx 48$ Hz, H-2), 4.44 (qd, $J_{4,5} = 0.8$, $J_{5,6} = 6.5$ Hz, H-5), 1.27 (d, 3H, $J = 6.5$ Hz, *C*-Me).

*Carminomycinone (30)*

Aglycon **10** was prepared (9*c*,*d*) by hydrolysis of carminomycin hydrochloride with aqueous 0.1 M HCl (30 min at 100°C). The red crystalline precipitate was washed well with water and dried in a desiccator; mp 235–236°C (lit. (9*c*) mp 233–235°C); $^1H$ nmr (200 MHz) δ: 13.43, 12.91, and 12.13 (3 s, 3 phenolic OH), 7.85, 7.68, and 7.28 (dd, t, and dd, 1H each, $J = 1.25$ and 8 Hz, H-1,2,3), 5.26 (m (dd after $D_2O$ exchange), $J_{7,8e} = 2$, $J_{7a,8a} = 5$ Hz, H-7), 4.61 (s, exchangeable, OH-9), 3.93 (d, exchangeable, $J_{7,OH} = 6.6$ Hz, OH-7), 3.17 (dd, $J_{8e,10e} = 2$, $J_{10a,10e} = 18.6$ Hz, H-10e), 2.94 (d, $J = 18.6$ Hz, H-10a), 2.39 (s, 3H, $CH_3$-14), 2.32 (dt, $J_{7,8e} = J_{8e,10e} = 2$, $J_{8a,8e} = 14.5$ Hz, H-8e), 2.14 (dd, $J_{7a,8e} = 5$, $J_{8a,8e} = 14.5$ Hz, H-8a).

*7-O-(4-O-Acetyl-2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-α-L-talopyranosyl)-carminomycinone (**11**)*

Aglycon **10** was dried overnight at 110°C in an oil-pump vacuum, and the solvents $CH_2Cl_2$ and ether were bidistilled from $P_2O_5$ and NaH, respectively. The reaction flask and granular molecular sieve 4A (3 g) contained therein were flame-dried and allowed to cool in a desiccator. The reaction was performed under $N_2$ with strict exclusion of atmospheric moisture. A solution of **8** (380 mg, 1.1 mmol) in $CH_2Cl_2$ (10 mL) and ether (8 mL) was placed over the molecular sieve, the mixture was cooled to −40°C, and trimethylsilyl triflate (0.84 mL) was introduced rapidly by syringe. The mixture was then stirred at 0°C for 1 h before **10** (525 mg, 1.4 mmol) in $CH_2Cl_2$ (15 mL) was added. Stirring was then continued at room temperature, and the reaction was monitored by tlc (solvent D), which revealed a gradual consumption of **8** ($R_f$ 0.45) and **10** ($R_f$ 0.1), and formation of **11** ($R_f$ 0.33) as the main product accompanied by traces of a minor product ($R_f$ 0.25). A moderate proportion of **8** appeared unreacted after 24 h; therefore, the mixture was cooled again to −40°C and stirred for 15 min with added trimethylsilyl triflate (0.1 mL), and **10** (100 mg) was then added at 0°C. Stirring was continued for a further 24 h at 25°C, but some **8** still persisted. The mixture was processed by shaking with ethyl acetate (150 mL) and saturated, aqueous $NaHCO_3$ (50 mL). The phases were separated, and the aqueous phase was extracted exhaustively with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on a column (30 g of $SiO_2$) with solvent E, to give unreacted **8** (125 mg, 33% recovery) followed by **11** (374 mg, 51%; 75.6% taking into account the recovered **8**). Compound **11** was a red powder, mp 156–166°C; $[\alpha]_D$ +168° (*c* 0.5, $CHCl_3$); $\nu_{max}^{KBr}$: 3520, 3440, 3320 (br), 1730, 1600 $cm^{-1}$; $^1H$ nmr δ: 13.35, 12.90, and 12.05 (3 s, 3 phenolic OH), 7.87, 7.70, and 7.31 (dd, t, and dd, $J \approx 1$ and 8 Hz, H-1,2,3), 6.71 (d, $J_{3',NH}$ = 8.3 Hz, NH), 5.58 (dd, $J_{1',2'}$ = 1.2, $J_{1',F} \approx 8$ Hz, H-1′), 5.27 (dd, $J_{7,8e} = 2$, $J_{7,8a} = 4.5$ Hz, H-7), 5.18 (nm, $W \approx 4$ Hz, H-4′), 4.65 and 4.49 (2 nm, 0.5H each, $J_{2',F}$ = 48.6 Hz, H-2′), 4.38 (qd, $J_{4',5'} \approx 1$, $J_{5',6'}$ = 6.5 Hz, H-5; the outer parts of the H-5 signal were overlapped by two dt, 0.5H each, for H-3′, with $J_{2',3'} \approx J_{3',4'} \approx 3$, $J_{3',NH} = 8$, $J_{3',F} \approx 34$ Hz), 3.85 (s, exchangeable, OH-9), 3.24 (dd, $J_{8e,10e}$ = 1.9, $J_{10a,10e}$ = 19 Hz, H-10e), 2.97 (d, $J$ = 19 Hz, H-10a), 2.41 (s, 3H, $CH_3$-14), 2.36 (dnm, with downfield nm partly obscured by $CH_3$-14 signal, $J_{8a,8e} \approx 16$ Hz, $J_{7,8e}$ and $J_{8e,10e} \approx 1$–2 Hz, H-8e), 2.19 (s, 3H, AcO-4′, superposed on H-8a signal), 1.23 (d, 3H, $J$ = 6.5 Hz, $CH_3$-6′); $^{13}C$ nmr (75.43 MHz, $CDCl_3$, assignments by aid of ADEPT experiment): (a) aglycon, δ: 210.3 (C-13), 190.1 and 185.7 (C-5,12), 162.3, 156.3, and 156.1 (C-4,6,11), 137.0, 124.8, and 119.6 (C-1,2,3), 136.4, 132.9, and 132.5 (C-6a,10a,12a), 115.6, 111.3, and 110.4 (C-4a,5a,11a), 76.0 (C-9), 71.3 (C-7), 35.4 and 33.2 (C-8,10), 24.6 (C-14); (b) carbohydrate moiety, δ: 170.8 (*Me*CO), 100.2 (d, $^2J_{1',F}$ = 31.4 Hz, C-1′), 85.1 (d, $^1J_{2',F}$ = 179.7 Hz, C-2′), 68.7 (s, C-4′), 65.9 (s, C-5′), 46.7 (d, $^2J_{3',F}$ = 16.2 Hz, C-3′), 20.6 (*CO*Me), 16.4 (s, C-6′). Quartets near δ 157 and 115 for the $CF_3CO$ group were too weak to be accurately determinable. Anal. calcd. for $C_{30}H_{27}F_4NO_{12}$ (669.5): C 53.82, H 4.07, N 2.09; found: C 53.89, H 4.11, N 1.98.

*7-O-(3-Amino-2,3,6-trideoxy-2-fluoro-α-L-talopyranosyl)-carminomycinone (**4**, (R)-2′-fluorocarminomycin) and its hydrochloride **4**a*

To a solution of **11** (360 mg) in methanol (50 mL) was added methanolic 1 M $NaOCH_3$ (5 mL), at room temperature, whereby the orange-red solution turned deep purple. After 1 h, saponification of **11** ($R_f$ 0.4) to (*R*)-2′-fluoro-*N*-trifluoroacetylcarminomycin **12** ($R_f$ 0.25) was complete (tlc with solvent D). The solution was neutralized with methanolic acetic acid, and evaporated, to give crude **12** as a brown solid. The solid was dissolved under $N_2$ in a saturated, aqueous $Ba(OH)_2$ solution (20 mL) at 25°C. After 30 min the purple mixture was neutralized by addition of solid carbon dioxide until an orange color persisted, diluted with water (10 mL), and extracted exhaustively with $CHCl_3$. The red extracts were dried ($MgSO_4$) and evaporated to give a brownish-purple solid that was triturated with a little fresh $CHCl_3$, isolated by suction filtration, and dried. The product (**4**-monohydrate, 244 mg, 82.6%) showed an elongated spot ($R_f$ 0.5–0.25) and a minor impurity ($R_f$ 0.7) in tlc (solvent C); mp 217–219°C, $\nu_{max}^{KBr}$: 3500, 3400, 1715, 1600 $cm^{-1}$; $^1H$ nmr δ: 7.87, 7.70, and 7.31 (dd, t, and dd, $J \approx 1$ and 8 Hz, H-1,2,3), 5.53 (dd, $J_{1',2'} \approx 1$, $J_{1',F} \approx 8.5$ Hz, H-1′), 5.28 (nm, H-7), 4.62 and 4.38 (2 nm, 0.5H each, $J_{2',F}$ = 48.5 Hz, H-2′), 4.16 (q, $J_{5',6'}$ = 6.5 Hz, H-5′), 3.48 (nm, H-4′), 3.23 (dd, $J_{8e,10e} \approx 1.5$, $J_{10a,10e}$ = 19 Hz, H-10e), 2.97 (d, $J$ = 19 Hz, H-10a, superposed on cm for H-3′), 2.40 (s, 3H, $CH_3$-14, superposed on m for H-8e), 2.17 (dd, $J_{7,8a}$ = 4, $J_{8a,8e}$ = 15 Hz, H-8a), 1.35 (d, 3H, $J$ = 6.4 Hz, $CH_3$-6′). Anal. calcd. for $C_{26}H_{26}FNO_{10}\cdot H_2O$ (549.5): C 57.77, H 5.03, N 2.59; found: 57.88, H 5.02, N 2.40.

For preparation of the *hydrochloride* **4***a*, a solution of **4** in 0.1 M HCl (40 mL) was first extracted with ethyl acetate for removal of the aforementioned impurity ($R_f$ 0.7), and then evaporated to dryness with additions of ethanol and benzene. The red solid obtained gave a single spot ($R_f$ 0.2) in tlc (solvent B). It was recrystallized from ethanol–ether and dried *in vacuo* over KOH, and weighed 173 mg (82.6%); mp 217–218°C (with sintering from 206°C); $[\alpha]_D$ +214 ± 15° (*c* 0.05, $CH_3OH$); $\nu_{max}^{KBr}$: 3400 (br), 1710, 1610 $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$) δ: 7.83 (m, 2H) and 7.43 (d, $J$ = 7.4 Hz) for H-1,2,3; 5.60 (s, exchangeable, OH-9), 5.41 (dd, $J_{1',2'}$ = 1.1, $J_{1',F}$ = 9.7 Hz, H-1′), 5.31 (d, $J_{4',OH}$ = 6.5 Hz, exchangeable, OH-4′), 5.06 (nm, H-7), 4.64 and 4.47 (2 nm, 0.5 H each, $J_{2',F}$ = 49.2 Hz, H-2′), 4.32 (~q, $J_{5',6'}$ = 6.6 Hz, H-5′), 3.62 (m, $W_H \approx 14$ Hz, narrowed further after $D_2O$ exchange, H-4′), 3.4 (H-3′, signal partly obscured by DOH peak), 2.96 (AB-q, 2H, H-10a,e), 2.30 (s, 3H, $CH_3$-14), 2.18 (m, 2H, H-8a,e), 1.22 (d, 3H, $J$ = 6.6 Hz, $CH_3$-6′); $^{13}C$ nmr (50.23 MHz, DMSO-$d_6$): (a) aglycon, δ: >200 (C-13, not observed), 190.3 and 186.3 (C-5,12), 161.7, 156.3, and 155.7 (C-4,6,11), 137.7, 124.9, and 119.3 (C-1,2,3), 137.1, 134.5, and 133.2 (C-6a,10a,12a), 116.0, 111.0, and 110.1 (C-4a,5a,11a), 74.7 (C-9), 70.8 (C-7), ~37.5 and 31.5 (C-8,10), 24.2 (C-14); (b) carbohydrate moiety, δ: 99.0 (d, $^2J_{1',F}$ = 31 Hz, C-1′), 80.4 (d, $^1J_{2',F}$ = 185 Hz, C-2′), 66.2 (C-4′), 65.6 (C-5′), 54.5 (d, $^2J_{3',F}$ = 16 Hz, C-3′), 16.2 (C-2′).

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