The synthesis of daunosaminyl ε-rhodomycinone, daunosaminyl 10-epi-ε-rhodomycinone, daunosaminyl ε-pyrromycinone, and 10-descarbomethoxy-ε-pyrromycin

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This paper is dedicated to the memory of Dr. Léo Marion

JOHN M. ESSERY and TERRENCE W. DOYLE. Can. J. Chem. **58**, 1869 (1980).

The epimerisation at C10 of ε-rhodomycinone by aqueous alkali treatment of its 6,7-acetonide is described. Daunosaminyl ε-rhodomycinone and daunosaminyl 10-epi-ε-rhodomycinone were prepared and compared with regard to their antibacterial properties. Daunosaminyl ε-pyrromycinone and 10-descarbomethoxy-ε-pyrromycin were synthesized and their antitumor properties were compared with some naturally occurring glycosides of ε-pyrromycinone.

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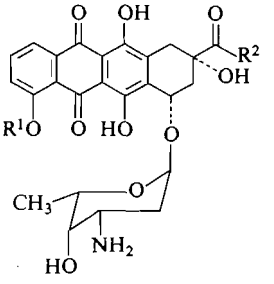
On décrit l'épimérisation, au niveau du carbone en position 10 de l'ε-rhodomycinone, à partir de son acétonide-6,7 sous l'influence d'une solution aqueuse de base. On a préparé la daunosaminyl ε-rhodomycinone et la daunosaminyl épi-10 ε-rhodomycinone et on les a comparé par rapport à leurs propriétés antibactériennes. On a synthétisé la daunosaminyl-ε-pyrromycinone et la descarbométhoxy-10 pyrromycine et on a comparé leurs propriétés anti-tumorales à celles de quelques glycosides de ε-pyrromycinone naturelles.

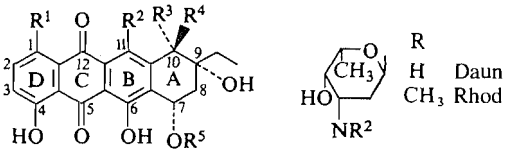
[Traduit par le journal]

The chemistry and biology of adriamycin (**1***a*) and the structurally related anthracyclines daunomycin (**1***b*) and carminomycin (**1***c*) have been extensively studied (1). Recently the isolation and characterization of a number of new anthracyclines which have considerable structural and biological differences from the adriamycin class of antitumor agents have been reported (2). Earlier communications from these laboratories have described a number of new agents based on the aglycone ε-



1*a* $R^1 = CH_3$, $R^2 = CH_2OH$
1*b* $R^1 = R^2 = CH_3$
1*c* $R^1 = H$, $R^2 = CH_3$

pyrromycinone (**2***a*) (2*a*–*d*). Oki and co-workers (2*e*–*g*) have reported additional members of this group as well as numerous antitumor agents based on the closely related aglycone aklavinone (**2***b*). Structurally there are a number of differences between the members of the aklavinone–pyrromycinone group and those of the adriamycin group. While the monosaccharides **1***a*–*c* are quite



	R^1	R^2	R^3	R^4	R^5
2*a*	OH	H	H	CO_2CH_3	H
2*b*	H	H	H	CO_2CH_3	H
2*c*	OH	H	H	CO_2CH_3	Rhod
2*d*	H	H	H	CO_2CH_3	Rhod
2*e*	OH	H	H	H	Rhod
2*f*	OH	H	H	CO_2CH_3	Daun
2*g*	H	OH	H	CO_2CH_3	Daun
2*h*	H	OH	CO_2CH_3	H	Daun
2*i*	H	OH	H	CO_2CH_3	H
2*j*	H	OH	CO_2CH_3	H	H

potent antitumor agents, it has been shown that pyrromycin (**2***c*) and aklavin (**2***d*) possess little or no antitumor activity (2*e*, 3). *A priori* a number of reasons may be advanced to explain this lack of activity: (*1*) the substitution of rhodosamine for daunosamine in the glycosides **2***c* and **2***d*; (*2*) the presence of a 10-carbomethoxy group in compounds **2***c* and **2***d*; and (*3*) the different oxygenation pattern in the anthraquinone portion of the molecule.

We have shown previously that removal of the 10-carbomethoxy function or epimerization at C10 in marcellomycin (**3***a*) resulted in compounds **3***b* and **3***c*, respectively. These compounds were significantly less active than **3***a* (2*b*, *d*). We would now like to report the syntheses of 10-descarbomethoxy-ε-pyrromycin (**2***e*), daunosaminyl

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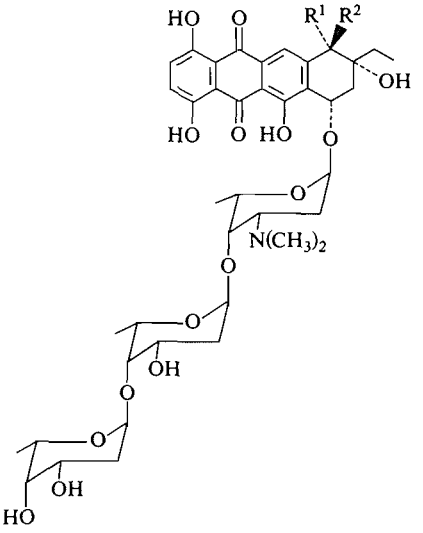


3*a* $R^1 = H, R^2 = CO_2CH_3$
3*b* $R^1 = R^2 = H$
3*c* $R^1 = CO_2CH_3, R^2 = H$

ε-pyrromycinone (**2***f*), daunosaminyl ε-rhodomycinone (**2***g*),[2] and daunosaminyl 10-epi-ε-rhodomycinone (**2***h*). We felt that a comparison of the activities of **2***c*, **2***e*, **2***f*, and **2***g* would permit an estimate of whether or not the lack of activity of pyrromycin was due to the amino sugar differences, the presence of the 10-carbomethoxy group, or the anthracycline oxygenation pattern. It has been shown that both ε-pyrromycinone (**2***a*) and ε-rhodomycinone (**2***i*) possess the absolute stereochemistry 7*S*,9*R*,10*R* (5, 6). It was suggested that the preferred conformation of ring A in **2***a* and **2***i* was that shown in partial structure **2***i* (Fig. 1), i.e. with the 10-carbomethoxy group pseudoaxial (5).

While in the pyrromycinone-based anthracyclines epimerization at C10 was readily effected by treatment with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) (2*c*), similar attempts with ε-rhodomycinone **2***i* failed completely. In the case of **3***a* the ratio of marcellomycin (**3***a*) to mimimycin (**3***c*) at equilibrium was 77:23. Presumably in the ε-rhodomycinone series the added steric effect of an 11-hydroxyl with the 10-carbomethoxy group in the 10*S* (pseudoequatorial) configuration was sufficient to displace the equilibrium completely towards the naturally occurring 10*R* configuration. In **2***i* the conformation of the A ring holds both the 7-hydroxyl and the 10-carbomethoxy groups in a pseudoaxial position. We suspected that if the 6,7-acetonide (**5***a*) could be formed, ring A would be forced into a conformation resulting in a steric interaction between the carbomethoxy group and the *peri*-phenolic group at C11. This steric strain could be relieved by epimerization at C10 as depicted in Fig. 1. Acid-catalyzed reaction of **2***i* with 2,2-dimethoxypropane gave as expected the 7,9-acetonide (**4**) (5). In the presence of *N*,*N*-dimethylformamide, however, there was obtained a mixture of **4** and the 6,7-acetonide (**5***a*) (Scheme 1) which was readily separated by column chromatography. Epimerization at C10 occurred when a chloroform solution of **5***a* was stirred with dilute aqueous sodium hydroxide to give a roughly 60:40 mixture of **5***a* and **5***b*. The epimer **5***b* was separated by silica gel chromatography and was characterized by the ^1H nmr spectrum. An upfield shift of 0.26 ppm for the resonance due to the C10 proton relative to that of **5***a* and a downfield shift of 0.06 ppm for the carbomethoxy resonance was observed. These are similar to the shifts found for the corresponding resonances in mimimycin (**3***c*) compared to marcellomycin (**3***a*) although in the present case the shift in the carbomethoxy resonance is smaller. Hydrolysis of **5***b* provided 10-epi-ε-rhodomycinone (**2***j*) which crystallized from methanol as red needles of mp 197–198°C. The infrared spectrum of **2***j*, in both the solid state and in solution, was very similar to that of **2***i* with absorptions due to the ester carbonyl at 1725 cm^{-1} and to the hydrogen-bonded quinone carbonyls at 1600 cm^{-1}. The uv–visible spectrum of **2***j* was also similar to that of **2***i* but with an additional absorption at 577 nm. The three phenolic protons gave singlets in the nmr spectrum at 13.5, 12.9, and 11.9 ppm, indicating hydrogen bonding to the quinone carbonyl groups. The signals due to the aromatic, ethyl, and C7 protons had similar chemical shifts to those in **2***i* although the line shape of the signal for the C7 proton was very similar to that seen in **5***b*, indicating a pseudoaxial orientation for this proton. The most notable differences in the spectra of **2***j*

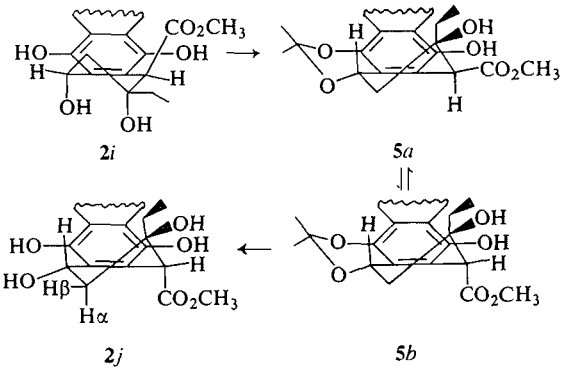
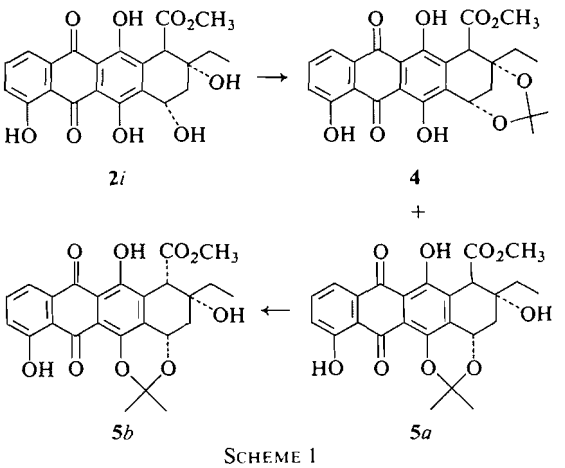


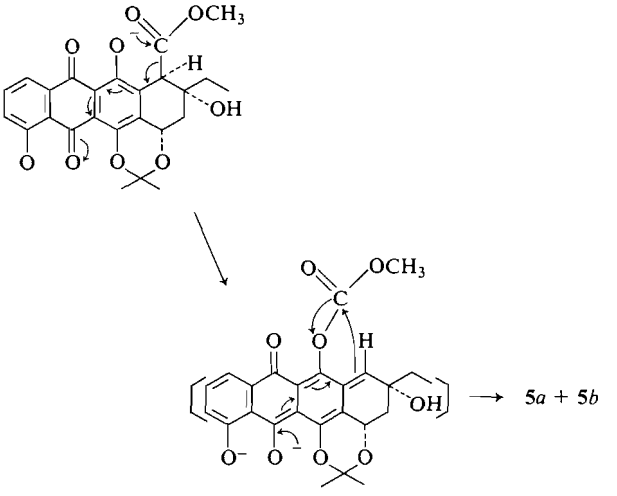
FIG. 1. Conversion of **2***i* to **2***j*.

[2]While our work was in progress the synthesis of **2***g* was reported (4).



SCHEME 1

and **2***i* were the upfield shift of 0.21 ppm of the C10 proton resonance and the change in both chemical shift and coupling constants for the C8 protons, the latter reflecting a change in conformation of the saturated ring. In this case, the carbomethoxy resonance was shifted upfield by 0.04 ppm relative to that in **2***i*. The ^{13}C spectrum of **2***j* was very similar to that of **2***i* (2*c*) there being only minor differences in most carbon resonances for the A ring. A shift of 1.7 ppm to higher field for the C9 resonance was the greatest shift observed. These properties showed **2***j* to be different from an aglycone, isolated from an unnamed *Streptomyces* species by Bowie and Johnson (7), called θ-rhodomycinone which they suggested was an isomer of ε-rhodomycinone. θ-Rhodomycinone, mp 220°C dec., had carbonyl absorptions at 1712, 1642, and 1622 cm^{-1} and it was postulated that the ester group was equatorial and hydrogen-bonded to the C11 phenolic group. The infrared and nmr spectral evidence clearly indicate that in **2***j* the C11 phenol is bonded to the C12 carbonyl and not to the ester. When the epimerization of **5***a* was carried out in a $CDCl_3$–D_2O–NaOD mixture, it was found by monitoring the course of the reaction via nmr spectra that the C10 proton did not exchange with the deuterium atoms present. This would seem to preclude proton abstraction at C10 as the mechanism for the epimerization, and leads us to postulate participation by the *peri*-phenol anion as follows:[3]



Relief of steric strain in the saturated ring is a consequence of the change in configuration of the ester group from pseudoequatorial (as in **5***a*, Fig. 1) to pseudoaxial, which lessens its interaction with the 9-ethyl and 11-hydroxyl groups. If this mechanism is operating, it would be expected that the corresponding epimerization would not occur with the 6,7-acetonide of ε-pyrromycinone which does not possess the necessary phenol function at C11. Unfortunately we were unable to prepare this compound. Reaction of **2***a* with 2,2-dimethoxypropane in the absence of DMF afforded the 7,9-acetonide **6**, and in the presence of DMF the only isolable products were the 7,9-acetonide and the known η-pyrromycinone (**7**) which resulted by elimination of water from **2***a* (Scheme 2). It was found that neither of the 7,9-acetonides **4** and **6** underwent base-catalyzed epimerization at C10.

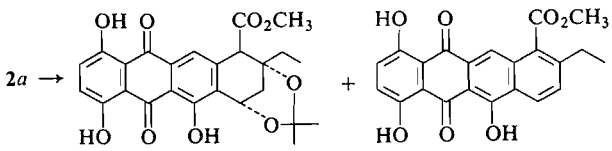
With the appropriate aglycones in hand i.e., **2***a*, **2***i*, and **2***j*, the conversion of these into their daunosamine glycosides was carried out. Following known procedures daunosamine (**8**) was converted to the *O*,*N*-protected bromo-sugar **9** (8) which was condensed with **2***i* to yield **2***g* (after removal of the protecting groups (8)) as its α-anomer. This was shown by the position (δ 5.5) and appearance (broadened singlet of half-band width 6 Hz) of the anomeric proton in the ^1H nmr spec-

TABLE 1. ^{13}C nmr shifts for selected carbons in **2***c* and **2***e*[a]

Carbon	**2***c*	**2***e*
C10	57.4 d	42.9 t
C9	71.8 s	70.0 s
C8	34.2 t	35.0 t
C7	71.1 d	70.8 d
C13	32.3 t	37.3 t
C14	6.7 q	7.4 q

[a]Recorded in $CDCl_3$ at 25.2 MHz. Chemical shifts are relative to internal TMS.

[3]A referee has pointed out that an alternate hypothesis, that of ClO—H proton abstraction followed by redelivery of the proton to the opposite face, may be operative.



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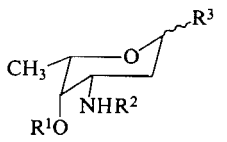
SCHEME 2

trum (9). Similarly 10-epi-ε-rhodomycinone (**2***j*) provided in low yield the α-glycoside **2***h*. For the conversion of ε-pyrromycinone (**2***a*) to its glycoside **2***f* the method of Arcamone *et al.* (10) using the *O*,*N*-bistrifluoroacetyl daunosaminyl chloride **10** was employed. This gave **2***f* in low yield following deprotection.



	R^1	R^2	R^3
8	H	H	OH
9	*p*-$NO_2C_6H_4CO$	$COCF_3$	Br
10	$COCF_3$	$COCF_3$	Cl

The synthesis of 10-descarbomethoxy-ε-pyrromycin (**2***e*) was accomplished using the method of Wiley *et al.* (11). Treatment of **2***c* with aqueous potassium hydroxide gave the crude 10-carboxylic acid which, when allowed to stand in dimethylformamide, decarboxylated to yield **2***e*. The structure of **2***e* was evident from its ^1H and ^{13}C nmr spectra. Thus the loss of signals for the C10 and carbomethoxy protons in **2***c* coupled with the appearance of an AB quartet at δ 1.99 for the C10 protons in **2***e* indicated that the desired conversion had been achieved. In the ^{13}C nmr spectrum the signal for C10 at δ 57.4 in **2***c* disappeared to be replaced by a methylene signal at δ 42.9 in **2***e*. The signals for C13 and C9 also showed significant shifts (Table 1).

Pyrromycin (**2***c*) has been shown previously to be marginally active against L-1210 leukemia (3). Both 10-descarbomethoxy-ε-pyrromycin (**2***e*) and daunosaminyl ε-pyrromycinone (**2***f*) were inactive in L-1210 leukemia and displayed lower antibacterial activity in a plate assay.[4] Previously Smith *et al.* (4) have shown that daunosaminyl ε-rhodomycinone **2***g* was 16-fold less active than **2***c*. This loss in potency parallels that observed in going from marcellomycin (**3***a*) to mimimycin (**3***c*). In the paper describing the synthesis of **2***g* (4) the synthesis and activity of 13-deoxydaunomycin was reported. This compound was less potent (~½) but had comparable activity to **1***b*.

[4]W. T. Bradner and M. Misiek, unpublished results. The plate assay is against *B. subtilis* ATCC 6633.

These results indicate that anthracyclines containing a carbomethoxy function at C10 and an ethyl group at C9 are inactive or marginally active antitumor agents when in the form of monosaccharides containing daunosamine or rhodosamine. For expression of significant activity, the substituent at C7 must be a di- or tri-saccharide, and maximum antitumor activity is associated with 10*R* stereochemistry. The lack of activity of 10-descarbomethoxy-ε-pyrromycin (**2***e*), in contrast to that of 13-deoxydaunomycin, may be a reflection of the deleterious effect of the hydroxyl group at C1.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 or XL-100 spectrometer using $CDCl_3$ as solvent (unless otherwise specified) and tetramethylsilane as internal standard. Infrared spectra were recorded as KBr disks on a Beckman IR-2420 and uv–visible spectra on a Beckman Acta III spectrophotometer.

ε-Rhodomycinone-7,9-acetonide (4) and -6,7-Actonide (5a)

A mixture containing 21.4 g of ε-rhodomycinone (**2***i*), 0.7 g of *p*-toluenesulfonic acid monohydrate, 350 mL of 2,2-dimethoxypropane, and 175 mL of dry DMF was heated under reflux with stirring for 17 h. Volatile components were removed under reduced pressure and the residue was triturated with $CHCl_3$ to provide 5.32 g of **4**. Recrystallization from $CHCl_3$ gave an orange solid, 252–253°C; nmr δ:13.47 (s, 1H, OH), 12.86 (s, 1H, OH), 12.26 (s, 1H, OH), 7.94–7.63 (m, 2H, C1—H and C2—H), 7.35 (dd, 1H, C3—H), 5.48 (m, 1H, C7—H), 4.25 (s, 1H, C10—H), 3.79 (s, 3H, CO_2CH_3), 2.42 (m, 2H, C8—H), 1.95–1.50 (m, 5H, CH_2—CH_3 and C—CH_3), 1.27–1.06 (m, 6H, CH_2—CH_3 and C—CH_3). *Anal.* calcd. for $C_{25}H_{24}O_9$: C 64.10, H 5.16; found: C 63.77, H 5.26.

The filtrate from **4** was evaporated and the residue chromatographed on 300 g of silica gel (Mallinckrodt CC-7) using chloroform as the solvent to give 0.44 g of **4** and then 17.7 g of a mixture containing **4** and **5***a*. This mixture was rechromatographed by the dry column technique on deactivated silica gel using $CHCl_3$–MeOH 95:5 as the solvent, and provided 1.70 g of **4** (total yield 7.46 g, 32%), 2.42 g (10%) of **5***a*, and 10.55 g (49%) of ε-rhodomycinone. Compound **5***a*, mp 164–165°C; ir: 1735, 1620 cm^{-1}; uv–visible (EtOH) λ_{max}:476 (ε15 000), 291 (10 800), 251 (sh 21 700), 234 (44 400); nmr δ:13.60 (s, 1H, OH), 13.01 (s, 1H, OH), 7.76–7.46 (m, 2H, C1—H, C2—H), 7.18 (dd obscured by solvent, C3—H), 5.06 (dd, J = 8 Hz, 1H, C7—H), 4.32 (s, 1H, C10—H), 3.71 (s, 3H, CO_2CH_3), 2.59 (dd, J = 8 Hz, 14 Hz, 1H, C8—H), 2.26–1.56 (m, 9H includes C8—H, CH_2CH_3, $C(CH_3)_2$), 1.08 (t, 3H, CH_2—CH_3). *Anal.* calcd. for $C_{25}H_{24}O_9 \cdot 1/4\ H_2O$: C 63.48, H 5.22; found: C 63.56, H 5.34.

10-epi-ε-Rhodomycinone-6,7-acetonide (5b)

A solution of 1.52 g of **5***a* in 75 mL of $CHCl_3$ was stirred for 16 h with 7.5 mL of 2.5% aqueous NaOH. The mixture was diluted with H_2O and acidified with HOAc. The $CHCl_3$ layer was separated, washed (H_2O), dried (Na_2SO_4), and evaporated to give 1.43 g of red foam. This was chromatographed on a dry column of 140 g of deactivated silica gel using $CHCl_3$–EtOAc 9:1 as the developing solvent to provide 228 mg of **5***a*, 450 mg of a mixture of **5***a* and **5***b*, and 600 mg of **5***b* as a red foam. A portion of this was crystallized from ether – Skellysolve B to give a red solid of mp 177–178°C. Infrared: 1740, 1615 cm^{-1}; uv–visible (EtOH) λ_{max}:475 (ε 10 400), 293 (6040), 250 (14 000), 234 (30 600); nmr δ: 7.81–7.50 (m, 2H, C1—H, C2—H), 7.25 (obscured by

solvent, C3—H), 5.26 (dd, J = 6 Hz, 11Hz, 1H, C7—H), 4.06 (s, 1H, C10—H), 3.79 (s, 3H, CO_2CH_3), 2.38 (dd, J = 6 Hz, 13 Hz, 1H, C8—H), 1.90–1.54 (m, 9H, includes C8—H, CH_2—CH_3, $C(CH_3)_2$), 1.01 (t, 3H, CH_2—CH_3). *Anal.* calcd. for $C_{25}H_{24}O_9 \cdot H_2O$: C 61.72, H 5.39; found: C 61.88, H 5.23.

10-epi-ε-Rhodomycinone (2j)

A solution of 550 mg of **5***b* in 40 mL of THF and 20 mL of 2 *N* HCl was stirred for 5 h. The solution was diluted with THF and washed with 2 × 10 mL portions of brine. The organic phase was dried (Na_2SO_4) and the solvent removed to give a red solid which was chromatographed on a dry column of deactivated silica gel using $CHCl_3$–MeOH 9:1 as the developing solvent. The major fraction consisted of **2***j* contaminated with traces of **2***i*. A 140 mg sample of pure **2***j* was obtained and recrystallization from methanol gave red needles of mp 197–198°C. Infrared ($CHCl_3$): 1725, 1600 cm^{-1}; uv–visible (EtOH) λ_{max}:577 (ε 9900), 531 (15 600), 495 (10 600), 295 (11 100), 251 (38 000), 234 (46 800); $[\alpha]_{578}^{23}$ +218° (*c* 0.05, THF); nmr δ: 13.48 (s, 1H, OH), 12.88 (s, 1H, OH), 11.87 (s, 1H, OH), 7.84–7.53 (m, 2H, C1—H, C2—H), 7.24 (dd partially obscured by solvent, C3—H), 5.20 (m, 1H, C7—H), 4.02 (s, 1H, C10—H), 3.72 (s, 3H, CO_2CH_3), 3.56 (bs, 1H, OH), 2.36 (dd, 1H, J_1 = 14, J_2 = 6 Hz, C8—Hα), 1.95 (dd, 1H, J_1 = 14, J_2 = 4 Hz, C8—Hβ), 1.68 (m, 2H, CH_2CH_3), 0.98 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C nmr (DMSO-d_6):189.6 (C5), 185.5 (C12), 170.39 (CO_2CH_3), 161.1 (C4), 155.2, 155.9 (C6, C11), 138.6 (C12a), 137.0 (C2), 134.7 (C10a), 132.8 (C6a), 124.3 (C1), 118.8 (C3), 115.7 (C4a), 110.4, 110.5 (C11a, C5a), 69.8 (C9), 61.0 (C7), 51.5 (CO_2CH_3), 51.0 (C10), 35.8 (C8), 32.8 (C13), 7.57(C14). *Anal.* calcd. for $C_{22}H_{20}O_9$: C 61.68, H 4.71; found: C 61.32, H 4.86.

Daunosaminyl ε-Rhodomycinone (2g)

To a stirred slurry of 143 mg (0.33 mmol) of ε-rhodomycinone, 500 mg (2.3 mmol) of yellow mercuric oxide, 103 mg (0.35 mmol) of mercuric bromide, and 3 g of powdered 3A molecular sieves in 40 mL of dry THF under reflux was added 0.33 mmol of a solution of the bromo-sugar **9** (prepared according to Acton *et al.* (8)) in 4 mL of THF. After the mixture had been heated for 20 h, an additional 0.33 mmol of **9** was added and after another 7 h another 0.33 mmol of **9** was added. After an additional 16 h under reflux, the mixture was allowed to cool and was filtered and the filtrate (and THF washings) were evaporated to a red foam. This was chromatographed on a dry column of deactivated silica gel to provide 825 mg of a mixture of **2***i* and product. Column chromatography on silica gel using $CHCl_3$–Et_2O 1:1 provided the desired product as the first fraction. Removal of the protecting groups (as in ref. 7) gave 64 mg of red solid. Column chromatography on silica gel with $CHCl_3$ removed impurities and **2***g* was eluted with $CHCl_3$–MeOH 1:1 to afford 32 mg (15%). Infrared: 1730, 1600 cm^{-1}; nmr δ: 7.88–7.56 (m, C1—H, C2—H), 7.26 (dd partially obscured by solvent, C3—H), 6.30 (broad, includes exchangeable protons), 5.50 (bs, peak width at 1/2 height 6 Hz, C1′-H), 5.25 (bs, C7—H), 4.3 (s, C10—H), 4.3–4.06 (m, C5—H), 3.76 (s, CO_2CH_3), 3.54 (bs, C4′—H), 3.18 (b, C3′—H), 2.40–2.24 (m, C8—H), 2.02–1.09 (m, includes C2′—H, CH_2—CH_3, C5′—CH_3, CH_2—CH_3). *Anal.* calcd. for $C_{28}H_{31}NO_{11} \cdot 2H_2O$: C 56.65, H 5.94, N 2.36; found: C 56.51, H 5.87, N 2.46.

Daunosaminyl 10-epi-ε-Rhodomycinone (2h)

Similarly, 143 mg (0.33 mmol) of 10-epi-ε-rhodomycinone (**2***j*) was reacted with 1 mmol of bromo-sugar (**9**) to provide 23 mg (12%) of **2***h*. Infrared: 1730, 1600 cm^{-1}; nmr ($CDCl_3$ + D_2O) δ: 7.95–7.56 (m, 2H, C1—H, C2—H), 7.28 (dd partially obscured by solvent, C3—H), 5.46 (bs, 1H peak width at 1/2 height 6 Hz, C1′—H), 5.14 (bm, 1H, C7—H), 4.22 (s, 1H, C10—H), 3.98 (q, 1H, C5′—H), 3.74 (s, 3H, CO_2CH_3), 3.65–3.32 (m, 2H, C3′—H, C4′—H), 2.6–0.8 (m, includes C8—H, C2′—H, CH_2—CH_3, C5′—CH_3). *Anal.* calcd. for $C_{28}H_{31}NO_{11} \cdot 0.5\ H_2O$: C 59.36, H 5.69, N 2.47; found: C 59.35, H 5.63, N 2.25.

Daunosaminyl ε-Pyrromycinone (2f)

A slurry of 214 mg (0.5 mmol) of ε-pyrromycinone (**2***a*), 428 mg (1.98 mmol) of yellow mercuric oxide, 107 mg (0.30 mmol) of mercuric bromide, and 1.0 g of powdered molecular sieves (3A) in 45 mL of ethanol-free $CHCl_3$ was stirred for 1 h. A solution of 1.2 mmol of the chloro-sugar (**10**, prepared according to Arcamone *et al.* (10)) in 10 mL of $CHCl_3$ was added in two equal portions 22 h apart. After a reaction time of 93 h, the mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 100 mL MeOH and heated under reflux for 30 min. The mixture was filtered and the filtrate evaporated to dryness. The residue was chromatographed on a dry column of deactivated silica gel using $CHCl_3$–MeOH 9:1 as the solvent to provide, as the fast-moving fraction, 15 mg of η-pyrromycinone (**7**), mp 218–220°C. The major fraction was a mixture of the aglycone (**2***a*) and the *N*-protected glycoside, and the latter crystallized from a concentrated solution of this mixture in $CHCl_3$. A solution of 100 mg of this glycoside in 10 mL of THF and 10 mL of 0.1 *N* NaOH was stored at 5°C for 4.5 h. The solution was diluted and the pH adjusted to 8.5. The product was extracted into $CHCl_3$ and the washed (H_2O) and dried (Na_2SO_4) extracts were evaporated to a purple solid which crystallized from ether to give 38 mg (14%) of **2***f*, mp 154–155°C. Infrared: 1735, 1600 cm^{-1}; nmr δ: 7.63 (s, 1H, C11—H), 7.20 (s, 2H, C2—H C3—H), 6.80 (b, 5H, exchangeable protons), 5.46 (s, 1H, peak width at half-height 6 Hz, C1′—H), 5.26 (s, 1H, C7—H), 4.30–4.06 (m, 2H, includes C5′—H, C10—H), 3.76 (s, 3H, CO_2CH_3), 3.50 (m, 1H, C4′—H), 3.15 (b, 1H, C3′—H), 2.70–2.24 (m, 2H, C8—H), 2.0–1.5 (m, 4H, C2′—H, CH_2—CH_3). 1.5–1.0 (m, 6H, C5′—CH_3—CH_2CH_3). *Anal.* calcd. for $C_{28}H_{31}NO_{11} \cdot H_2O$: C 58.43, H 5.78; found: C 58.32, H 5.72.

10-Descarbomethoxypyrromycin (2e)

A solution of 1.17 g (2 mmol) of pyrromycin (**2***c*) in 10 mL of 0.53 *N* potassium hydroxide was let stand 16 h at ~23°C. The solution was diluted with 20 mL of water and the pH was adjusted to 5.9 with 2 *N* hydrochloric acid. The slurry was filtered and the resulting solid washed with water. The combined mother liquors were lyophilized. Both solids (1.113 g) were combined, dissolved in 30 mL of dimethylformamide, and let stand for 18 h. The solvent was removed at reduced pressure and the resulting gum chromatographed on 15 g of silica gel (10% by weight of water added) using chloroform as eluent. Fractions were collected visually and assayed by tlc. In addition to a number of unidentified by-products, there was obtained 83 mg of η-pyrromycinone (**7**) and 642 mg of crude **2***e*. Compound **2***e* was rechromatographed on silica gel (10% by weight of water added) using chloroform–methanol (9:1) as eluent to yield 140 mg of **2***e* mp 188–190°C; ^1H nmr ($CDCl_3$) δ: 7.56 (s, 1H, C11—H), 7.25 (s, 2H, C2—H + C3—H), 5.50 (bs, 1H, C1′—H), 5.20 (bs, 1H, C7—H), 2.5–3.2 (m, 3H, C3′, C4′, C5′H's), 1.99 (AB quartet, 2H, C10—H's), 2.27 (s, 6H, $N(CH_3)_2$), 1.5–2.0 (m, 6H, C8, C13, C2′H's), 1.43 (d, 3H, C5′—CH_3), 1.09 (t, 3H, CH_2CH_3); ^{13}C nmr ($CDCl_3$) δ:190.1 (C5), 185.6 (C12), 161.7 (C6), 158.0, 157.4 (C1, C4), 145.6 (C10a), 132.0 (C6a), 130.7 (C11a), 129.6, 129.4 (C2, C3), 120.7 (C11), 113.5 (C5a), 112.4, 112.1 (C4a, C12a), 100.7 (C1′), 70.8 (C7), 70.0 (C9), 66.5, 65.9 (C4′, C5′), 60.0 (C3′), 42.0 (C10), 41.9 (NMe_2), 37.3 (C13), 35.0 (C8), 28.4 (C2′), 17.0 (C6′), 7.4 (C14). *Anal.* calcd. for $C_{28}H_{33}NO_9 \cdot 3/2\ H_2O$: C 60.64, H 6.50, N 2.53; found: C 59.84, H 6.26, N 2.66.

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