Pergamon

Tetrahedron Vol. 50, No. 4, pp. 1165-1172, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0050-P

Synthesis and Cytotoxic Activity of New 4'-Deoxy C-3'-Homo Anthracyclines

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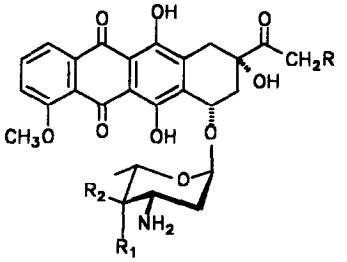
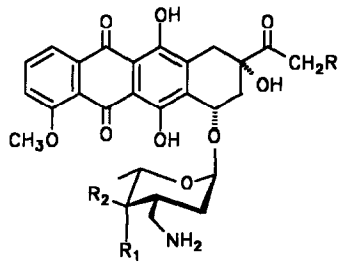
Abstract: Starting from (S)-propylene oxide, the protected C-3 homolog of 4-deoxy daunosamine **11** is prepared in 4 steps. Acid catalyzed glycosidation of anthracyclinones such as daunomycinone, β-rhodomycinone and ε-isorhodomycinone with **11** affords new analogs of anthracyclines demonstrating strong cytotoxicity against L1210 leukemia, A-549 and HT-29 tumor cells.

INTRODUCTION

The clinical efficiency of anthracycline antibiotics, and particularly of doxorubicin **1a**,[1] in anticancer chemotherapy has induced numerous studies to improve the therapeutic index of this class of compounds. In this respect, modification of the sugar moiety of anthracyclines has been particularly fruitful leading to improved analogs such as epirubicin (4'-epi doxorubicin) **2**,[2] pirarubicin (4'-0-tetrahydropyranyl doxorubicin) **3**[3] or esorubicin (4'-deoxy doxorubicin) **4**.[4]



1a Doxorubicin R=R_1=OH, R_2=H
1b Daunorubicin R=R_2=H, R_1=OH
2 4'-epi doxorubicin R=R_2=OH, R_1=H
3 Pirarubicin R=OH, R_1=OTHP, R_2=H
4 Esorubicin R=OH, R_1=R_2=H



5a R=R_2=H, R_1=OH
5b R=R_1=OH, R_2=H
6a R=R_1=H, R_2=OH
6b R=R_2=OH, R_1=H

All these compounds display a reduced cardiotoxicity compared to **1** in clinical trials. Other modifications giving highly active analogs, not implying the C-4' hydroxyl, have been described: replacement of the C-3' NH_2 group by OH,[5] introduction of a 2'-iodo[6] or 2'-fluoro[7] substituent or alkylation of the primary amine function[8] (including the formation of the potent morpholino analogs[9]).

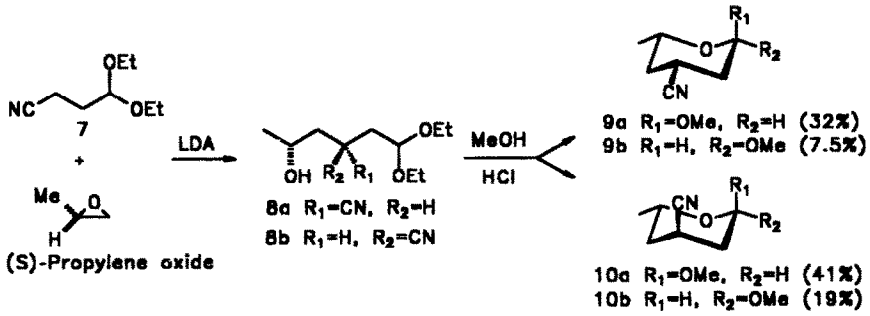
A new type of modification has been suggested by Pullman[10] on the basis of intercalation models of daunorubicin **1b** with the double-stranded oligonucleotide $d(CGATCG)_2$. Since there is a correlation between the stability of the DNA-anthracycline complex and antitumor activity of the corresponding anthracycline, these authors have suggested the synthesis and evaluation of new analogs, such as **5a,b**, bearing a $-CH_2NH_2$ group instead of the amino group at C-3'. The increase in affinity estimated as δ (difference of the resulting energy balance ΔE, which is the sum of the intermolecular interaction energy (ΔE_{inter}) and of the conformational energy change of the anthracycline (ΔE_{conf}), between this analog and **1b**) is estimated to be as high as 15 kcal/mol and may be due to better electrostatic interactions of the protonated amine (more imbedded in the minor groove) with the DNA backbone.

Subsequently, a patent[11] has described the synthesis of analogs such as **6a,b** (including the C-3' epimers) in the 4'-epi series using as the key step the condensation of nitromethane with methyl-2,6-dideoxy-α-L-*erythro*-hexapyranosid-3-ulose followed by reduction of the corresponding nitroalkene. However only the cytotoxicity and antitumor activity of the C-3' epimer (prepared by silver triflate catalyzed condensation of the corresponding 1-chloro derivative) has been reported.

Taking into account this hypothesis and the observation that esorubicin **4** is more active and less cardiotoxic than **1a**, the synthesis of 4'-deoxy C-3'-homoanthracyclines seems worthwhile and thus the preparation of the suitable carbohydrate derivative **12** was first carried out followed by the glycosidation of known anthracyclinones, such as daunomycinone, β-rhodomycinone and ϵ-rhodomycinone.

PREPARATION OF METHYL GLYCOSIDE 12.

Commercially available cyanopropionaldehyde diethyl acetal **7** is treated with LDA in THF at -78°C and the resulting anion is then reacted with (S)-propylene oxide (1.3 eq) to give an unseparable mixture of the two epimeric hydroxy nitriles **8a,b** in 98% isolated yield. HPLC analysis (Lichrosorb Si 60 7μ, eluent hexane-AcOEt, 7:3) shows that the **a/b** ratio is 40/60 and this is in agreement with the observation of signals at δ 2.89 and 3.05 ppm (in similar relative intensity), corresponding to the α-cyano proton.



Methanolysis of this mixture affords four compounds which are separated by chromatography over silica to give by decreasing polarity order: **10a** (41%), **9b** (7.5%), **10b** (19%) and **9a** (32%). The overall ratio of **10a,b/9a,b** is similar to the 60/40 ratio observed for **8a,b** thus allowing the structure determination of the major nitrile formed in the epoxide condensation. Structures of the four methyl glycosides are consistent with their ^1H NMR spectra (Table 1).

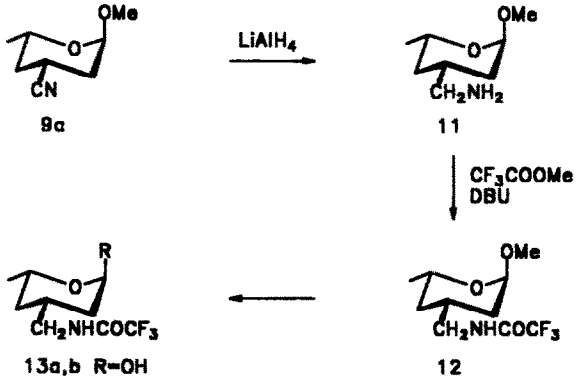
Table 1. ^1H NMR spectra ($CDCl_3$, δ in ppm, mult., J in Hz) of glycosides **9a,b** and **10a,b**.

Compound	CHCN	H-5	H-1
9a	3.08	3.82	4.76
	tt (11.5, 3.5)	m	s (W_H= 6)
9b	2.75	3.50	4.30
	tt (12, 5)	-*	dd (9, 2)
10a	3.03	4.18	4.76
	s (W_H=11.5)	sext.d (6, 2)	s (W_H= 6)
10b	3.17	3.92	4.75
	s (W_H= 10)	sext.d (7.5, 2)	dd (10, 2.5)

*: partly hindered, sext.: sextuplet

As expected the amount of the more stable α anomers (**9a** and **10a**) accounts for 73% of the mixture. The configuration of the nitrile group is easily determined by the signal of the corresponding proton and by the relative deshielding of the C-5 proton in the case of the axial isomers (CN anisotropy).

However the amount of the desired isomer **9a** may be increased by base-catalyzed equilibration of the methanolysis mixture prior to chromatography, a stable 80/20 ratio of **9a,b/10a,b** being reached after treatment with tBuOK (0.4 eq.) in tBuOH for 12 h at room temperature.

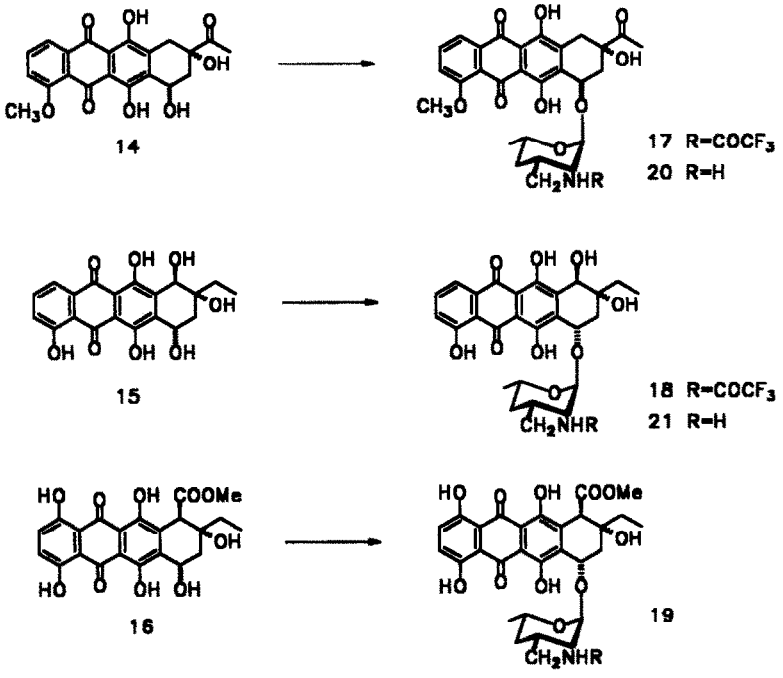


$LiAlH_4$ reduction of nitrile **9a** affords the primary amine **11** (91%) as a yellow oil. This material could not be converted to trifluoroacetamide **12** under the standard trifluoroacetic anhydride-pyridine conditions since no material could be recovered probably due to extensive decomposition. However treatment of **11** with methyl trifluoroacetate in presence of DBU affords the desired amide **12** in 76% yield.

GLYCOSIDATION

Glycosidation reactions of anthracyclinones have been reported under different conditions, including the Koenigs-Knorr procedure using 1-bromo 2-deoxy carbohydrates, readily prepared with HBr from the corresponding 1-O-acyl derivative or glycal, or by direct Lewis or protonic acid-catalyzed condensation of the 1-O acyl derivative. However all attempts to prepare these derivatives failed in our case. Acid catalyzed hydrolysis of **12** affords a 80/20 mixture of the α and β anomers **13a** and **13b** in 95% yield from which the corresponding acetates could be obtained (Ac_2O, cat. H_2SO_4, 20°C, 48h) in only 30% isolated yield.[12] Furthermore attempted treatment of the latter with HBr to get the 1-bromo derivative or thermal or SiO_2-catalyzed elimination of acetic acid to afford the corresponding glycal failed.

These disappointing results, and particularly the easy formation of by-products, probably arise from the high reactivity of the hemiacetal together with the possible participation of the $-CH_2NHCOCF_3$ group. The observation that the tetrahydropyran ring bears no oxygenated group at C-2 or C-4 as in carbohydrates and that the 3-NHCOR is replaced by a less deactivated group $-CH_2NHCOR$ clearly suggests that the formation of the corresponding oxonium ion is easier in this case.



These considerations prompted us to attempt an acid-catalyzed transglycosidation of the methyl glycoside **12** with anthracyclinones in presence of 4 Å molecular sieves as methanol trap. Reactions were carried out in anhydrous CH_2Cl_2 in presence of anhydrous PTSA (increasing amounts 0.1 to 0.5 eq.) using 1 eq. of **12** and Daunomycinone **14**, β-Rhodomycinone **15** and ε-isorhodomycinone **16**. In each case a single glycoside **17-19** is obtained in isolated yields ranging from 10-16% (~60% based on recovered aglycones). The structures of these new glycosides are consistent with their MS and ^1H NMR spectra. For example, the signals for H-1 and H-7 appear respectively at δ 5.54 and 5.31 ppm in the case of **17** in good agreement with the chemical shifts observed for 4-deoxydaunomycin (δ 5.59 and 5.30 ppm). Similar values are observed in the case of **19** (δ 5.49 and 5.25 ppm) and of **18** (δ 5.47 and 5.14 ppm). In the case of the β-Rhodomycinone, the formation of a 10-O-glycoside instead of the less hindered 7-O-glycoside **18** may be ruled out on the basis of the chemical shift for H-10 in **18** (δ 4.85 ppm) and β-rhodomycinone (δ 4.87 ppm) which is lower than for 10-O-glycosides (i.e. δ 4.99 ppm in the case of a 7,10-bis-α-L-fucopyranosyl derivative[13]).

CYTOTOXIC ACTIVITY

Compounds **17-19** were tested *in vitro* against L1210 leukemia, A-549 and HT-29 tumor cells (MTT reduction Assay) as well as compounds **20** and **21** obtained by base-catalyzed hydrolysis of **17** and **18** (immediately before testing). The results summarized in Table 2 show that (the ε-isorhodomycinone glycoside **19** is much less active with IC_{50}'s higher than 1 μg/mL) the glycosides obtained from β-Rhodomycinone and Daunomycinone are highly active and that glycoside **20** demonstrate an activity in the same range as Doxorubicin (the C-3' epimer of **6a** has also been reported[11] to display IC_{50} values against HeLa and P388 cells similar to those observed for daunorubicin).

Table 2. Cytotoxicity (IC_{50} in μg/mL) in the MTT assay.[14]

Compound	L1210	A-549	HT-29
Doxorubicin	0.02	0.05	0.06
17	0.25	0.67	0.43
18	0.14	0.48	0.14
20	0.04	0.10	0.04
21	0.11	0.13	0.13

CONCLUSION

Starting from the hypothesis of Pullman, new 4'-deoxy anthracyclines bearing a 3'-CH_2NHR group instead of the usual aminogroup have been prepared from (S)-propylene oxide. The preliminary results obtained for the *in vitro* activity against L1210, A-549 and HT-29 seems to substantiate the initial hypothesis. Further experiments such as DNA binding measurements and in vivo activity tests are however needed to precise the biological properties of this new kind of glycosides.

ACKNOWLEDGMENTS

We thank Laboratoires HOECHST (Paris) and CNRS for financial support and Dr. H.H. Sedlacek (Behringweke AG, Marburg, FRG) for a generous gift of anthracyclines and for biological testing.

EXPERIMENTAL

Melting points were measured with a Tottoli Buchi 510 apparatus and are uncorrected. IR spectra were recorded on a Beckman, Acculab 2 spectrophotometer. ^1H NMR spectra were obtained on a Brucker WP 200 SY spectrometer using $CDCl_3$ as a solvent and TMS as as internal standard. Microanalyses were obtained from the "Service Central de Microanalyses" (CNRS, Lyon).

3(R,S)-cyano 1,1-diethoxy 5(S)-hexanol 7a,b.

To a solution of diisopropylamine (4.6 mL, 32.8 mmol) in anhydrous THF (32.4 mL) (kept at -10°C under N_2) was slowly added nBuLi (20.5 mL of a 1.6 M solution in hexane). After stirring the resulting colourless mixture at -10°C during 30 min and then cooling at -78°C, a solution of 3-cyanopropionaldehyde diethylacetal (4.32 g, 27,5 mmol) in anhydrous THF (2 mL) was slowly added and stirring was then continued for 2 h at -78°C. At the same temperature, propylene oxide (2.04 g, 1.3 eq.) was added and the mixture was stirred overnight while slowly warming to room temperature. The reaction mixture was then pourred into a solution of saturated NH_4Cl and extracted with ether. The combined extracts were dried over Na_2SO_4 and after removal of the solvent, the residue was rapidly filtered over SiO_2 (eluent : hexane-AcOEt, 7:3) to give **7a, b**(5.8 g, 98%) as a yellow oil which was used in the next step without further purification.
^1H NMR ($CDCl_3$): δ 1.23 (9H, t), 1.68 (2H, m), 1.89 (2H, m), 2.28 (1H, m), 2.89 (0.5H, p, J=6.5Hz), 3.05 (0.5H, h, J=4.5 Hz), 3.65 (4H, m), 4.01 (1H, m), 4.70 (1H, t) ppm.

Methyl glycosides 8a,b and 9a,b.

To a solution of **7a,b** (2.55 g, 11.8mmol) in anhydrous MeOH (12.5 mL) was added, at room temperature and under a N_2 atmosphere, a 0.92N solution of HCl in anhydrous MeOH (13 mL). The reaction was stopped when TLC (eluent : hexane-AcOEt, 4:1) indicated consumption of starting material (16 h) and the formation of four new compounds. After hydrolysis with a saturated $NaHCO_3$ solution and extraction with ether, the combined ether phases were washed with water and dried over Na_2SO_4. Evaporation under reduced pressure of ether, afforded a residue whose chromotography over SiO_2 (progressive elution with hexane-AcOEt, 98:2 to 80:20) yielded successively **9a** (32%), **10b** (19%), **9b** (7.5%) as oils and **10a** (41%, mp 61°C). The overall yield of the cyclisation was 82% from **8a,b**.
Note: Ethyl glycosides are detected by NMR at shorter reaction time.

Methyl 3-cyano-2, 3, 4, 6-tetradeoxy-α-L-*lyxo*hexopyranoside 9a.

oil; $[\alpha]_D^{20}$ -126 (c 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) : 1.2 (3H, d, J=7Hz, H-6), 1.53 (1H, q, J=11.5 Hz, H-4ax), 1.82 (1H, td, J_1=11.5Hz, J_2=3.5 Hz, H-2ax), 2.0 (2H, m, H-2eq and H-4eq), 3.08 (1H, tt, J_1=3.5Hz, J_2=11.5Hz, H-3), 3.33 (3H, s, OMe), 3.82 (1H, m, H-5), 4.76 (1H, s, W_H=6Hz, H-1) ppm; I.R. ($CHCl_3$) : 2220 cm^{-1} (CN). Anal.: calc. for $C_8H_{13}NO_2$: C 61.91, H 8.41; found: C 61.64, H 8.49.
NMR and IR data of the other isomers are given below:

Methyl 3-cyano-2, 3, 4, 6-tetradeoxy-β-L-*ribo*hexopyranoside 10b.

^1H NMR ($CDCl_3$): 1.3 (3H, d, J=6Hz, H-6), 1.36 (2H, m, H-4, H-2), 1.84 (1H, dd, J_1=9Hz, J_2=2Hz, H-2), 2.04 (1H, dd, J_1=9Hz, J_2=2Hz, H-4), 3.17 (1H, s, W_H=10Hz, H-3), 3.52 (3H, s, OMe), 3.92 (1H, sext.d, J_1=7.5Hz, J_2=2Hz, H-5), 4.75 (1H, dd, J_1=9.5Hz, J_2=2.5Hz, H-1) ppm; I.R. ($CHCl_3$) : 2240 cm^{-1} (CN).

Methyl 3-cyano-2, 3, 4, 6-tetradeoxy-β-L-*lyxo* hexopyranoside 9b

^1H NMR ($CDCl_3$): 1.28 (3H, d, J=6Hz, H-6), 1.44-1.61 (2H, m, H-4, H-2), 1.95 (1H, md, J=12.5Hz, H-4), 2.05 (1H, md, J=12.5Hz, H-2), 2.75 (1H, tt, J_1=5Hz, J_2=12Hz, H-3), 3.50 (3H, s, OMe),4.27 (dd, J_1=9.5Hz, J_2=2.5Hz, H-1) ppm; I.R. ($CHCl_3$): 2240 cm^{-1} (CN).

Methyl 3-cyano-2, 3, 4, 6-tetradeoxy-α-L-*ribo*hexopyranoside 10a
mp 61°C; $[\alpha]_D^{20}$ -152 (c 1.19, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.21 (3H, d, J=6Hz, H-6), 1.56 (1H, m,), 1.81 (2H, m,), 2.0 (1H, m,), 3.03, (1H, s, W_H=11.5Hz, H-3), 3.38 (3H, s, OMe), 4.18 (1H, sext.d, J_1=6Hz, J_2=2Hz, H-5), 4.76 (1H, s , W_H=6Hz, H-1) ppm; I.R. ($CHCl_3$): 2260 cm^{-1} (CN).

Base catalyzed equilibration of 10a
A solution of **10a** (0.126g, 0.82 mmol) in dry tBuOH (2 mL) was stirred in presence of tBuOK (0.036g, 0.4 eq.) at room temperature for 12h. HPLC analysis (column: Lichrosorb Si-60, 7μ, eluent: hexane-ethyl acetate, 70/30, V/V) gives a **9a/10a** ratio of 82/18. Identical figures were obtained after 72h at room temperature or at reflux.

Methyl 3-aminomethyl-2, 3, 4, 6-tetradeoxy-α-L-*lyxo*hexopyranoside 11
To a suspension of $LiAlH_4$ (0.23 g) in anhydrous THF (8.4 mL) was added slowly a solution of **9a** (0.83 g, 5.33 mmol) in THF (16.4 mL). After stirring the reaction mixture for 4 h at room temperature, TLC indicated consumption of starting material. Hydrolysis was performed by slow addition of a 10% solution of KOH (1.3 mL). The precipitated inorganic salts were filtered off and washed with AcOEt. Evaporation of the solvent afforded amine **11** (0.77 g, 91%) as a yellow oil which was used in the next step without purification.
^1H NMR ($CDCl_3$): 0.90 (1H, q, J= 12Hz, H-4ax), 1.17 (3H, d, J= 7Hz, H-6), 1.31 (2H, m), 1.8 (3H, m), 2.51-2.55 (2H, dd, J_1= 7Hz, J_2= 2Hz, CH_2N), 3.35 (3H, s, OMe), 3.85 (1H, m, H-5), 4.77 (1H, s, H-1) ppm.

Methyl N-trifluoroacetyl 3-aminomethyl-2, 3, 4, 6-tetradeoxy-α-L-*lyxo* hexopyranoside 12
The amine **11** (0.77 g, 4.84 mmol) was dissolved in methyl trifluoroacetate (27 ml, 55 eq.) in presence of DBU (0.26 mL, 0.35 eq.). The reaction mixture was stirred at room temperature overnight under N_2. After removal of CF_3COOMe under reduced pressure, chromatography over SiO_2 (Eluent: 3% MeOH-CH_2Cl_2) of the crude product afforded **12** (0.94 g, 76%) as a white powder.
mp 67°C; $[\alpha]_D^{20}$ -90.4 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.01 (1H, q, J= 11.5Hz, H-4ax),1.19 (1H, d, J= 7Hz, H-6), 1.29 (1H, td, J_1= 3Hz, J_2= 11.5Hz, H-2ax), 1.70 (2H, m, H-4eq and H-2eq), 2.20 (1H, broad s, W_H= 23Hz, H-3), 3.20 (2H, t, J= 6Hz, CH_2NH-), 3.34 (3H, s, OMe), 3.85 (1H, sept., J= 6Hz, H-5), 4.77 (1H, broad s, W_H= 7Hz, H-1), 7.21 (1H, broad s, W_H= 14Hz, NH) ppm; I.R. ($CHCl_3$): 3440 (NH), 3020, 2980 and 2940 (C-H), 1720 (C=O), 1540 (NH), 1450, 1385, 1225, 1160 and 1120 (C-O) cm^{-1}; Anal.: calcd. for $C_{10}H_{10}NO_3F_3$: C 47.06, H 6.32; found: C 47.33, H 6.21.

General procedure for the glycosidation reaction.
To a solution of the aglycone (0.26 mmol) in anhydrous CH_2Cl_2 (40 mL) kept under nitrogen, was added 4 Å molecular sieves (0.1 g) and anhydrous PTSA (0.1 eq.). The resulting mixture was then stirred for 30 min. A solution of methyl glycoside (1 eq.) in anhydrous CH_2Cl_2 (2 mL) was then added dropwise and the reaction was followed by TLC (eluent 3% MeOH-CH_2Cl_2). After 3 h, another 0.5 eq. of PTSA was added while stirring was continued for an additionnal 24 h. The mixture was hydrolyzed and extracted with CH_2Cl_2. The combined organic layers were washed successively with a saturated $NaHCO_3$ solution and water. After usual workup, the aglycone-glycoside mixture was separated on preparative plates (eluent 2% MeOH-CH_2Cl_2).

(7S,9R)-7-[[3-(Trifluoroacetamidomethyl)-2,3,4,6-tetradeoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-acetyl-4-methoxy-5,12-naphtacenedione 17
mp 84-85°C; $[\alpha]_D^{20}$ 206.9 (c 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.25 (m, 3H), 2.42 (s, 3H), 2.9 (d, J= 15Hz, 1H), 3.23 (t, J= 7Hz, 2H), 4.06 (s, 3H), 4.78 (s, 1H), 5.31 (s, 1H), 5.54 (s, 1H), 6.36 (broad s,1 H), 7.41 (d, J= 8Hz, 1H), 7.78 (t, J= 8Hz, 1H), 8 (d, J= 8Hz, 1H), 13.28 (s, 1H), 13.98 (s, 1H) ppm; I.R. (CH_2Cl_2): 3680 and 3420 (OH), 3060 (CH), 1730 (C=O), 1620 and 1580 (C=C), 1260, 1210 and

1170 (C-O) cm^{-1}. MS (70 eV): 621, 399, 398, 382, 380, 363, 362, 339, 337, 321, 309, 301. HRMS calcd. for $C_{30}H_{30}O_{10}NF_3$ 621.18215 found 621.18218.

(7S,9R)-7-[[3-(Trifluoroacetamidomethyl)-2,3,4,6-tetradeoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-4,6,9,10,11-pentahydroxy-9-ethyl-5,12-naphtacenedione 18
mp 95-97°C; $[\alpha]_D^{20}$ 192.5 (c 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.11 (t, J=7Hz, 3H), 1.26 (d, J=6Hz, 3H), 3.19 (m, 2H), 4.16 (m, 2H), 4.87 (s, 1H), 5.14 (s, 1H), 5.47 (s, 1H), 6.53 (s, W_H=11Hz, 1H), 7.30 (d, J=6Hz, 1H), 7.68 (t, J=8Hz, 1H), 7.78 (d, J=6Hz, 1H), 12 (s, 1H), 12.73 (s, 1H), 13.5 (s, 1H) ppm; I.R. (CH_2Cl_2): 3680, 3600, 3520 and 3440 (OH), 1725 (C=O), 1620, 1580 and 1550 (C=C), 1290, 1265, 1230, 1200 and 1165 (C-O) cm^{-1}; HRMS: calcd. for $C_{29}H_{30}O_{10}NF_3$ $[M+H]^+$: 610.18998; found 610.19000.

(7S,9R,10R)-7-[[3-(Trifluoroacetamidomethyl)-2,3,4,6-tetradeoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-1,4,6,9,11-pentahydroxy-10-carbomethoxy-9-ethyl-5,12-naphtacenedione 19
mp 186°C; $[\alpha]_D^{20}$ -140 (c 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.12 (t, 3H), 1.25 (d, H), 3.21 (m, 2H), 3.7 (s, 3H), 4.11 (m, 1H), 4.57 (s, 1H), 5.25 (s, 1H), 5.49 (s, 1H), 6.31 (s, 1H),12.29 (s, 1H) , 12.95 (s, 1H) ppm; HRMS: calcd. for $C_{31}H_{32}O_{12}NF_3$ 667.18763; found 667.18766.

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(*Received in Belgium* 18 *June* 1993; *accepted* 11 *October* 1993)