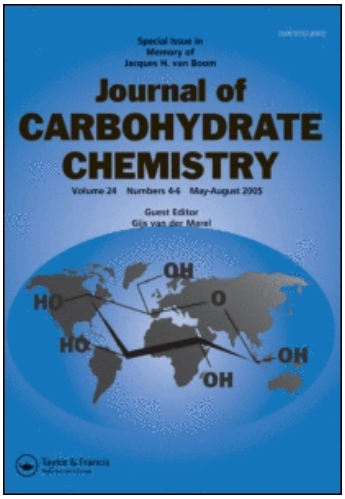

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SEMISYNTHETIC ε-ISORHODOMYCINS:

GLYCOSYLATION AND MODIFICATION REACTIONS[1]

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ABSTRACT

The syntheses of 7-O-α-L-daunosaminyl-ε-isorhodomycinone (6) and 7-O-α-L-rhodosaminyl-ε-isorhodomycinone (7) are described. The glycosyl donors 1,4-di-O-p-nitrobenzoyl-3-N-trifluoroacetyl-α,β-L-daunosamine and 1,4-di-O-acetyl-α,β-L-rhodosamine have proven to be the most suitable for the glycosylation of ε-isorhodomycinone (ε-iso RMN) (3), using the TMS triflate method. Deblocking (0.5 N NaOH) of the protected glycoside 4 led to the desired 7-O-glycosyl-ε-isorhodomycinones 5 and 6. The daunosaminyl glycoside 6 was methylated (CH_2O, $NaCNBH_3$) to provide the rhodosaminyl derivative 7. The photolytic demethylation of this product selectively provided the 7-O-(3'-N-methyl-α-L-daunosaminyl)-ε-isorhodomycinone (8).

INTRODUCTION

The anthracycline glycoside type antibiotics doxorubicin, daunorubicin and several analogues are extensively used in the chemotherapy of various cancers. How-

ever, chemotherapy employing these agents is hampered by a number of undesired side effects, the most serious being dose-related cardiotoxicity.[2,3] As part of our efforts to prepare related compounds having improved therapeutic properties, we now report the results of our studies on a number of synthetic approaches to ε-isorhodomycins.

As far as the ε-isorhodomycinone glycosides are concerned, only few reports on the synthesis of the glycosidic linkage have been published. El Khadem et al. prepared ε-rhodomycins by allowing ε-RMN to react with a large excess of the O-acetylated sugar halide in the presence of mercuric bromide, mercuric cyanide, and molecular sieve in tetrahydrofuran at reflux temperature.[4] The synthesis of 7-O-α-L-daunosaminyl-ε-RMN was described by Smith et al., who showed that the condensation of ε-RMN with 4 equiv. of 1-chloro-4-O-p-nitrobenzoyl-3-N-trifluoroacetyl-daunosamine stereoselectively results in the α-glycoside.[5]

On the other hand, the aglycones could be microbiologically glycosylated. The mutant KE 303, derived from streptomyces galilaeus, produced cinerulosyl-deoxyfucosyl-rhodosaminyl rhodomycinones by feeding the culture with the aglycones.[6]

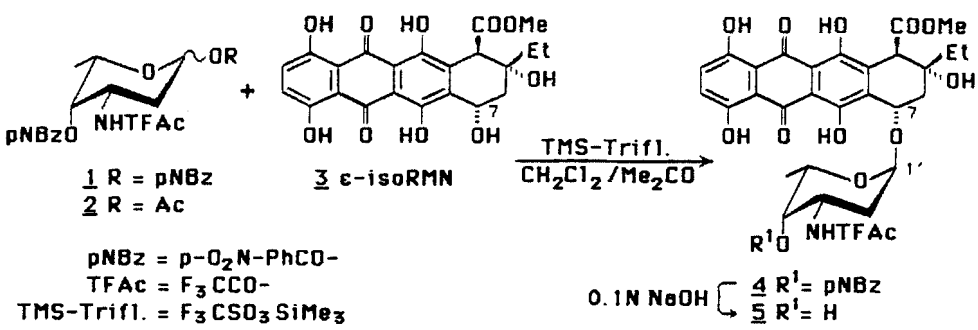
RESULTS AND DISCUSSION

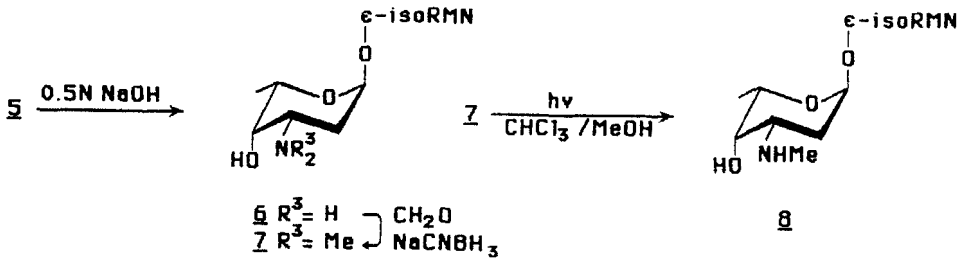
The procedure for coupling the daunosamine donors to anthracyclinones involved initial preparation of a suitably protected and glycosidically activated derivative of the sugar. These coupling precursors typically are N-trifluoroacetylated and protected at the 4-hydroxyl group by substituents such as trifluoroacetate or p-nitrobenzoate, and the anomeric position is activated for coupling either by the glycal or the glycosyl halide.[3] Kimura et al. found that the glycosylation of anthracyclinones with 1,4-di-O-p-nitrobenzoyl-N-trifluoro-acetyl-L-daunosamine (1) can efficiently be achieved by using trimethylsilyl

triflate to give the desired α-glycoside in almost quantitative yields.[7]

After several preliminary experiments, p-nitrobenzoate 1 and acetate 2 were chosen as the most promising daunosamine donors for the glycosylation of ε-isorhodomycinone.[8,9] In the presence of TMS triflate in dichloromethane-acetone, the desired α-glycoside 4 can be obtained from 1 or 2 in 76-82 % yield. For the synthesis of the glycoside the solubility of the reaction components, especially of the ε-isoRMN, and the reaction temperature are of particular importance. The reactions in dichloromethane or dichloromethane-diethylether provided only an approx. 30 % yield of α-glycoside.[7] At higher temperatures (>-10°C) one obtains the 7,9-bis-O-daunosaminyl derivative in addition to the desired 7-O-daunosaminyl compound 4. It was possible to interpret the ^{1}H NMR spectrum of 4 to a large extent with the aid of 2D-COSY experiments. The important features here are the down-field shift of H-1' to δ 5.60 in comparison to the α-methyl glycoside (δ 4.76) and the occurrence of small coupling constants and the OH-9 signal of δ 3.88, which is not present after the H/D exchange.

The protected compound 4 can be deblocked either partially to provide 5 by cleaving the p-nitrobenzoyl group with 0.1 N NaOH or completely to provide 6 by using 0.5 N NaOH. Under the conditions of reductive alkylation 6 is converted to 7-O-α-L-rhodosaminyl-ε-isoRMN (7) by formaldehyde and sodium cyanoborohydride.



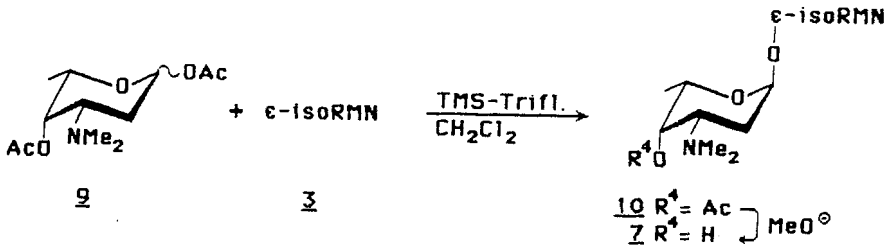


Compound 7, dissolved in chloroform, was found to be unstable under the action of sunlight, decomposing to form in particular the partially demethylated product 8. A specific attempt was made to photolytically mono-demethylate 7 to 8 by irradiating a solution of 7 in chloroform-methanol using a 500 Watt lamp and this produced 8 in reasonable yield.[11]

A 2D-COSY experiment was used to assign the protons within the ^{1}H NMR spectrum of 8. The characteristic signal of the N-methyl group appears at δ 2.39 and thus is at the same position as the signal of the dimethylamino group of educt 7. The FAB mass spectrum of 8 shows the expected molecule ion [M + H$^+$] (m/z = 588).

We succeeded in developing a new, direct method for the production of 7-O-α-L-rhodosaminyl-ε-isoRMN 7. In the following glycoside synthesis step, 1,4-di-O-acetyl-L-rhodosamine (9)[10] as a glycosyl donor is reacted with ε-isoRMN (3). In the presence of TMS triflate in dichloromethane the desired α-linked glycoside 10 is obtained in 55 % yield. The occurrence of ß-glycosidically linked product was not observed. Compound 10 is hydrolyzed by the method of Zemplén to split off the O-acetyl group. A comparison of the reaction product with compound 7 showed that it was identical to 7.

The rhodosamine component frequently occurs in microbial rhodomycins as well as in many other antibiotics. For this reason, the modified process presented here for the direct synthesis of α-rhodosaminides seems to be of particular interest.



9 3

EXPERIMENTAL

General Procedures. Reactions were carried out at ambient temperature unless otherwise stated. Solutions were concentrated under diminished pressure below 40°C (bath temperature). Melting points were determined on a Büchi melting point apparatus and are reported uncorrectedly. ^{1}H NMR spectra were recorded at 300 MHz or at 400 MHz on a Bruker AC-300 or a Bruker AM-400 NMR spectrometer, respectively. Chemical shifts for ^{1}H resonances were recorded relative to tetramethylsilane (0.0). In some cases the ^{1}H resonances were assigned by ^{1}H,^{1}H-COSY experiments, using the standard pulse sequences of the Bruker Aspect-300 software. Specific rotations were determinded by a Perkin Elmer Polarimeter-241. Reactions were monitored by TLC on silica gel plates 60 F 254 (Merck) and spots were detected by ultraviolet light or by spraying with concentrated sulfuric acid and subsequent heating to 150°C. The glycosylation reactions were performed under an argon cover in the presence of molecular sieve (4Å). Preparative chromatography was performed on silica gel (Merck Kieselgel 60 particle size 0.015-0.040 mm) with the solvent systems specified.

7-O-(4-O-p-Nitrobenzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (4) via p-nitrobenzoate 1. 1,4-Di-O-p-nitrobenzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α,β-L-lyxohexopyranose (1, 2.2 g, 4.06 mmol) and molecular sieve 4Å (1 g) were added to a stirred solution of ε-isorhodomycinone (3, 1.0 g, 2.25 mmol) in dry dichloromethane-aceton (100 ml, 10:1).

The suspension was cooled to -20°C. Trimethylsilyl trifluoromethanesulfonate (3.78 g, 17.00 mmol) was then added dropwise. The mixture was stirred overnight at -20°C. Triethylamine (8.3 ml) was added to the reaction mixture, which was then stirred for further 10 min more. The reaction mixture was filtered, and the residue on the filter was washed with dichloromethane. The organic solutions were washed with water and dried over anhydrous sodium sulfate. The residue obtained by evaporation of the solvent was chromatographed on a column of silica gel (190 g) with 5:5:1 dichloromethane-petrolether-acetone to give 1.51 g (82 %) of compound 4 as an amorphous solid: mp 195-197°C; $[\alpha]_D^{25}$ + 135.0° (c 0.1, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, $J_{13,14}$ = 7.5Hz, H-14), 1.21 (d, 3H, $J_{5',6'}$ = 6,5 Hz, H-6'), 1.43 (m, 1H, $J_{13a,14}$ = 7.5 Hz, $J_{13a,13b}$ = 15 Hz, H-13a), 1.80 (m, 1H, $J_{13b,14}$ = 7.5 Hz, $J_{13a,13b}$ = 15 Hz, H-13b), 2.04 (ddd, 1H, $J_{1',2'a}$ = 3.6 Hz, $J_{2'a,2'e}$ = 12.6 Hz, $J_{2'a,3}$ = 12.6 Hz, H-2'a), 2.10 (d, 1H, $J_{2'a,2'e}$ = 12.6 Hz, H-2'e), 2.24 (dd, 1H, $J_{7,8a}$ = 4 Hz, $J_{8a,8b}$ = 15 Hz, H-8a), 2.32 (d, 1H, $J_{8a,8b}$ = 15 Hz, H-8b), 3.67 (s, 3H, OMe), 3.88 (s, 1H, OH-9), 4.26 (s, 1H, H-10), 4.43 (m, 1H, H-3'), 4.44 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 5.22 (br s, 1H, H-7), 5.42 (br s, 1H, H-4'), 5.60 (d, 1H, $J_{1',2'a}$ = 3.6 Hz, H-1'), 6.31 (d, 1H, $J_{3',NH}$ = 7 Hz, NH), 7.22 (s, 2H, H-2, H-3), 8.23 (d, 2H, $J_{o,m}$ = 9 Hz, p-NBz), 8.27 (d, 2H, $J_{o,m}$ = 9 Hz, p-NBz), 12.20 (s, 1H, PhOH), 12.21 (s, 1H, PhOH), 12.73 (s, 1H, PhOH), 12.94 (s, 1H, PhOH). FAB-MS, m/z = 818 (M^+).

7-O-(4-O-p-Nitrobenzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (4) via acetate 2. Starting from ε-isorhodomycinone (3, 1g, 2.25 mmol) and 1-O-acetyl-4-O-p-nitrobenzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α,β-L-lyxohexopyranose (2, 2.17 g, 5 mmol), compound 4 was prepared as described in the previous procedure for the preparation of compound 3, but in this case the reaction solvent used was a 1:1 dichloromethane-acetone solvent mixture.

7-O-(2,3,6-trideoxy-3-trifluoroacetamido-α-L-lyxo-hexopyranosyl)-ε-isorhodomycinone (5). Compound 4 (80 mg, 0.097 mmol) was dissolved in 2:1 chloroform-methanol (2 mL), and aqueous 0.1 N NaOH solution (2 mL) was added. After 10 min, the reaction mixture was neutralized with 0.1 N HCl solution (2 mL). The product obtained after evaporation of the solvent was then purified on a short silica gel (50 g) column with 95:15:1:0.25:0.1 chloroform-acetone-acetic-acid-water-triethylamine to give 50 mg (76 %) of compound 5: mp 155-157°C, $[\alpha]_D^{25}$ + 560° (c 0.1, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, H/D Change) δ 1.05 (t, 3H, $J_{13,14}$ = 7.5 Hz, H-14), 1.22 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 1.38 (m, 1H, $J_{13a,13b}$ = 15 Hz, $J_{13a,14}$ = 7.5 Hz, H-13a), 1.78 (m, 1H, $J_{13a,13b}$ = 15 Hz, $J_{13b,14}$ = 7.5 Hz, H-13b), 1.83-1.90 (m, 2H, H-2'a, H-2'e), 2.14 (dd, 1H, $J_{7,8a}$ = 4.4 Hz, $J_{8a,8b}$ = 15 Hz, H-8a), 2.28 (d, 1H, $J_{8a,8b}$ = 15 Hz, H-8b), 3.30 (br s, 1H, H-4'), 3.64 (s, 3H, OMe), 4.08 (m, 1H, H-3'), 4.13 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 4.22 (s, 1H, H-10), 5.15 (d, 1H, $J_{7,8a}$ = 4.4 Hz, H-7), 5.40 (br s, 1H, H-1'), 7.26 (s, 2H, H-2 and H-3). FAB-MS, m/z = 669 (M^+), m/z = 692 ($M+Na^+$).

7-O-(3-Amino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (6). Compound 4 (0.81, 1 mmol) was deblocked with 0.5 N NaOH to give compound 6 in accordance with the procedure described previously for the preparation of compound 5. Yield of the title compound 6: 0.436 g (76 %); mp 178-180°C, $[\alpha]_D^{25}$ + 405° (c 0.1 methanol) ^{1}H NMR (300 MHz, $CDCl_3$/MeOD 5:1) δ 1.05 (t, 3H, $J_{13,14}$ = 7.2 Hz, H-14), 1.24 (d, 3H, $J_{5',6'}$ = 6.6 Hz, H-6'), 1.38 (m, 1H, $J_{13a,13b}$ = 14.6 Hz, $J_{13a,14}$ = 7,2 Hz, H-13a), 1.77 (m, 1H, $J_{13a,13b}$ = 14.6 Hz, $J_{13b,14}$ = 7.2 Hz, H-13b), 1.91 (br s, 2H, H-2'a, H-2'e), 2.15 (dd, 1H, $J_{7,8a}$ = 4 Hz, $J_{8a,8b}$ = 15 Hz, H-8a), 2.27 (d, 1H, $J_{8a,8b}$ = 15 Hz, H-8b), 3.15 (m, 1H, H-3'), 3.57 (br s, 1H, H-4'), 3.64 (s, 3H, OMe), 4.06 (q, 1H, $J_{5',6'}$ = 6.6 Hz, H-5'), 4.18 (s, 1H, H-10), 5.13 (br s, 1H, H-7), 5.41 (br s, 1H, H-1'), 7.25 (s, 2H, H-2, H-3), 12.25 (s, 2H, PhOH), 12.79 (s, 1H,

PhOH), 12.97 (s, 1H, PhOH). FAB-MS, m/z = 574 ($M+H^+$). Anal. Calcd for $C_{28}H_{31}NO_{12}$:C, 58.6; H, 5.4; N, 2.4. Found: C, 58.3; H, 5.5, N, 2.3.

7-O-(3-Dimethylamino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (7). Compound 6 (300 mg, 0.52 mmol) was dissolved in methanol (100 ml). Aqueous formaldehyde solution (1 ml, 37 % CH_2O) and sodium cyanoborohydride (300 mg) were added, and the reaction mixture was stirred for 3 d. It was then evaporated to dryness, and the resulting residue was purified by chromatography on silica gel (20 g) with 7:1 chloroform-methanol to give 225 mg (72 %) of compound 7: m.p. 178-180°C; $[\alpha]_D^{25}$ + 121° (c 0.1, methanol), ^1H NMR (300 MHz, DMF-d_7) δ 1.03 (t, 3H, $J_{13,14}$ = 7.5 Hz, H-14), 1.29 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 1.48 (m, 1H, $J_{13a,13b}$ = 14.0 Hz, $J_{13a,14}$ = 7.5 Hz, H-13a), 1.79 (m, 1H, $J_{13a,13b}$ = 14.0 Hz, $J_{13b,14}$ = 7.5 Hz, H-13b), 2.00 (br s, 2H, H-2'a, H-2'e), 2.16 (dd, 1H, $J_{7,8a}$ = 4,5 Hz, $J_{8a,8b}$ = 14,5 Hz, H-8a), 2.38 (d, 1H, $J_{8a,8b}$ = 14,5 Hz, H-8b), 2.40 (s, 6H, NMe_2), 2.59 (m, 1H, H-3'), 3.72 (s, 3H, OMe), 3.84 (br s, 1H, H-4'), 4.19 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 3.70 (s, 1H, H-10), 5.13 (d, 1H, $J_{7,8a}$ = 4.5 Hz, H-7), 5.45 (br s, 1H, H-1'), 7.24 (s, 2H, H-2, H-3). FAB-MS, m/z = 602 ($M+H^+$).

7-O-(3-Methylamino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (8). A solution of compound 7 (62 mg, 0.103 mmol) in a mixture of chloroform (100 ml) and methanol (5 ml) was transferred to a Petri dish of 19 cm diameter on a reflecting underlay and was then exposed to a 500 watt lamp at a distance of about 5 cm for 1 h at 0°C. The solvent was then removed in a rotary evaporator, the residue was dissolved in a minimum of methanol. Water was added, the pH was adjusted to 4.4 with 1 % strength hydrochloric acid, and the methanol was removed in a rotary evaporator. The remaining aqueous solution was extracted three times with chloroform. The combined chloroform phases were back-extracted three times with water of pH 4.5 and then with water of pH 9.5 and were

dried over sodium sulfate and filtered. The solvent was removed in a rotary evaporator and the residue was purified by repeated dissolving in dichloromethane and precipitation by addition of hexane to give 26 mg (43 %) of compound 8: m.p. 187°C; $[\alpha]_D^{25}$ + 143° (c 0.1, methanol), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J_{13,14}$ = 7.3 Hz, H-14), 1.37 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 2.39 (br s, 3H, NMe), 2.81 (br d, 1H, $J_{2',3'}$ = 10 Hz, H-3'), 3.72 (s, 3H, OMe), 4.10 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 4.28 (s, 1H, H-10), 5.25 (d, 1H, $J_{7,8}$ = 2.0 Hz, H-7), 5.49 (d, 1H, $J_{1',2'}$ = 2.5 Hz, H-1'), 7.30 (s, 2H, H-2 and H-3). FAB-MS, m/z = 588 ($M+H^+$).

7-O-(4-O-Acetyl-3-dimethylamino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (10). ε-Isorhodomycinone (3, 1 g, 2.25 mmol) was dissolved in anhydrous dichloromethane (200 ml). 1,4-Di-O-acetyl-3-dimethylamino-2,3,6-trideoxy-α,β-L-lyxohexopyranose (0.65 g, 2.53 mmol) and a molecular sieve (4Å, 5 g) in dichloromethane (20 ml) were added to this solution at room temperature, and the mixture was then stirred for 0.5 h. Then, trimethylsilyl trifluoromethanesulfonate (0.6 ml) was added. After 0.5 h, saturated sodium bicarbonate solution (60 ml) was added to the mixture. The organic phase was separated, washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on a column of silica gel (80 g) with 10:1 toluene-methanol to give 0.8 g (55 %) of compound 10. m.p. 209-210°C; $[\alpha]_D^{25}$ + 560° (c 0.05, chloroform); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J_{13,14}$ = 7.5 Hz, H-14), 1.18 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 1.46 (m, 1H, $J_{13a,13b}$ = 15 Hz), $J_{13a,14}$ = 7.5 Hz, H-13a), 1.86 (m, 1H, $J_{13a,13b}$ = 15 Hz, $J_{13b,14}$ = 7.5 Hz, H-13b), 1.93 (d, 1H, $J_{2'a,2'e}$ = 13Hz, H-2'e), 1.98 (ddd, 1H, $J_{1',2'a}$ = 3.5 Hz, $J_{2'a,2'e}$ = 13 Hz, $J_{2'a,3'}$ = 13 Hz, H-2'a), 2.18 (s, 3H, Ac), 2.19 (s, 6H, NMe_2), 2.33 (dd, 1H, $J_{7,8a}$ = 3.5 Hz, $J_{8a,8b}$ = 15 Hz, H-8a), 2.34 (d, 1H, $J_{8a,8b}$ = 15 Hz, H-8b), 2.35 (m, 1H, H-3'), 3.73 (s, 3H, OMe), 4.18 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 4.28 (br s, 1H,

H-10), 4.47 (s, 1H, OH-9), 5.26 (br s, 1H, H-7), 5.27 (br s, 1H, H-4'), 5.57 (br s, 1H, H-1'), 7.32 (s, 2H, H-2 and H-3), 12.31, 12.32, 12.84 and 13.01 (4s, 4H, PhOH). FAB-MS, m/z = 644 ($M+H^+$).

7-O-(3-Dimethylamino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-ε-isorhodomycinone (7) via deacetylation of 10. Compound 10 (0,5 g, 0.77 mmol) was dissolved in anhydrous methanol (100 mL) and a sodium methylate solution (0.1 mL, 30 %) was added. After stirring at room temperature for 2 h, the mixture was neutralized with Dowex WX8 ion exchange resin. It was then filtered and the filtrate was concentrated in vacuo to give 0.35 g (90 %) of compound 7. HPLC analysis revealed that this compound was identical to compound 7 discribed previously. Anal. Calcd for $C_{30}H_{35}NO_{12}$: C, 59.87; H, 5.86; N, 2.33. Found: C, 59.97; H, 5.91; N, 2.13.

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REFERENCES

1. Presented at the XIVth International Carbohydrate Symposium, Stockholm 1988, Abst. Pap. B 118.

2. H. S. El Khadem, Anthracycline Antibiotics, Academic Press; New York 1982.

3. F. Arcamone, Doxorubicin, Academic Press; New York 1981.

4. H. S. El Khadem, D. L. Swartz and R. C. Cermak, J. Med. Chem., 20, 957 (1977).

5. T. H. Smith, A. N. Fujiwara and D. W. Henry, J. Med. Chem., 21, 280 (1978).

6. T. Oki, in Anthracycline Antibiotics, H. S. El Khadem, Ed.j Academic Press: New York, 1982, p 75.

7. Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe and S. Terashima, Chemistry Letters, 501 (1984).

8. E. M. Acton, A. N. Fujiwara and D. W. Henry, J. Med. Chem., 17, 659 (1974).

9. H. S. El Khadem, A. Liav and D. L. Swartz, Carbohydrate Res., 74, 345 (1979).

10. H. Brockman, E. Spohler and T. Waehneldt, Chem. Ber., 96, 2295 (1963).

11. Presented at the IVth European Carbohydrate Symposium, Darmstadt, 1987, Abst. Pap. A 144.