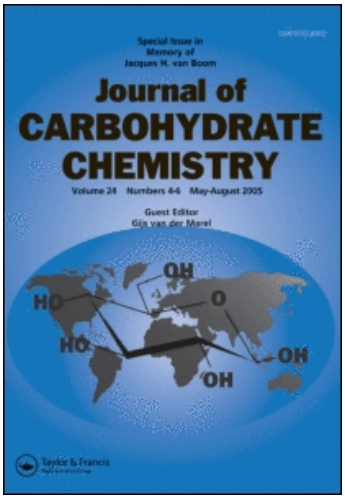

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Gerken, Manfred , Blank, Sabine , Kolar, Cenek and Hermentin, Peter(1989) 'Synthesis of 2'-Iodo Analogues of β-Rhodomycins[1]', Journal of Carbohydrate Chemistry, 8: 2, 247 — 254
To link to this Article: DOI: 10.1080/07328308908048007
URL: http://dx.doi.org/10.1080/07328308908048007

J. CARBOHYDRATE CHEMISTRY, 8(2), 247-254 (1989)

SYNTHESIS OF 2'-IODO ANALOGUES OF β-RHODOMYCINS [1]

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Received January 8, 1989 - Final Form January 24, 1989

ABSTRACT

10-*O*-(*R/S*)Tetrahydropyranosyl-β-rhodomycinone (**5a,b**) was prepared via 7,9-*O*-phenylboronyl-β-rhodomycinone (**3**) from β-rhodomycinone (**1**). Glycosidation of **5a,b** with 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (3,4-di-*O*-acetyl-L-rhamnal) (**6**) and 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (3,4-di-*O*-acetyl-L-fucal) (**7**) using *N*-iodosuccinimide gave the corresponding 7-*O*-glycosyl-β-rhodomycinones **8a,b**, **9a,b** and **10a,b**, **11a,b**. After cleavage of the THP-ether and O-deacetylation 7-*O*-(2,6-dideoxy-2-iodo-α-L-*manno*-hexopyranosyl)-β-rhodomycinone (**14**) and 7-*O*-(2,6-dideoxy-2-iodo-α-L-*talo*-hexopyranosyl)-β-rhodomycinone (**16**) were obtained.

INTRODUCTION

Anthracyclines like doxorubicin (adriamycin), daunorubicin (daunomycin) or epirubicin are among the most widely used cytostatics used in clinical cancer chemotherapy.[2] Because of the limited therapeutic range of these drugs and their severe toxic side effects we started our program on modified anthracycline glycosides, using the β-rhodomycinone aglycone, first described by Brockmann *et al.* in 1950.[3]

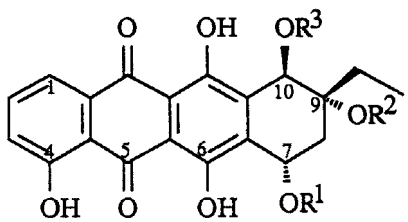
Because anthracycline antibiotics bearing 3-amino glycosides [4] are more common in nature, our research program focused on the modification of the sugar component. Thus the preparation of non-amino sugar glycosides, like those synthesized by Horton *et al.* for daunomycinone and adriamycinone,[5] using the *N*-iodosuccinimide (NIS) glycosidation method of Thiem *et al*[6] is the topic of the present communication. Some of these derivatives have shown high antitumor activity *in vivo*. For example 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-*manno*-hexopyranosyl)-daunomycinone, when tested in

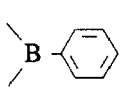
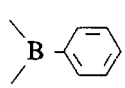
the murine P-388 lymphocytic leukemia model, has shown a T/C value of 247 (50 mg/kg).[5]

RESULTS AND DISCUSSION

In our efforts to gain access to semisynthetic 2,3,6-trideoxy-3-aminoglycosides of β-rhodomycinone, we originally focused on the glycosidation of 10-*O*-trifluoroacetyl-β-rhodomycinone (2) with appropriate 3-amino-glycosyl donors,[4] using the trimethylsilyl-triflate procedure. [7] Using the same aglycone we next tried to synthesize 2'-iodo-glycosides of β-rhodomycinone, employing the NIS method. [6] However this approach proved unsuccessful. We found that a new protecting group at the 10-position of the aglycone had to be used in order to obtain regioselective glycosidation at the 7-position of β-rhodomycinone.

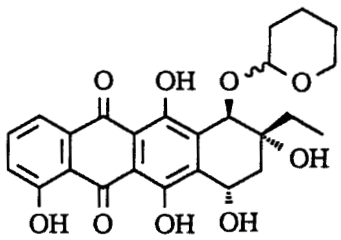
Reacting 3,4-dihydro-*2H*-pyran with the cyclic phenylborate ester **3** [4] in the presence of *p*-toluenesulfonic acid in dichloromethane gave the *R/S* diastereoisomers **4a,b**, which were immediately used for the next step without purification. Cleavage of the phenylborate ester yielded the corresponding aglycones **5a,b**. In the ^{1}H NMR spectrum of these *R/S* diastereoisomers two signals for each proton (a,b) were generally observed, although overlap to a single signal was sometimes observed.



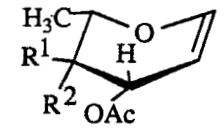
	1	2	3	4a,b	5a,b
R^1	H	H			H
R^2	H	H			H
R^3	H	$COCF_3$	H		

10-*O*-Tetrahydropyranyl-β-rhodomycinone (**5a,b**), with its free hydroxy group at positions 7 and 9, was suitable for glycosidation with 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (3,4-di-*O*-acetyl-L-rhamnal)[8] (**6**) in acetonitrile using

SCHEME 1



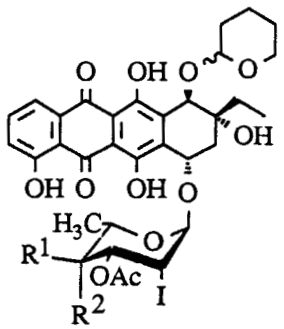
5a,b



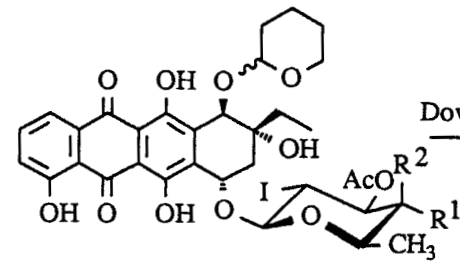
NIS / CH_3CN

6 = 3,4-Di-O-Ac-L-Rhamnal, R^1=OAc, R^2=H

7 = 3,4-Di-O-Ac-L-Fucal, R^1=H, R^2=OAc



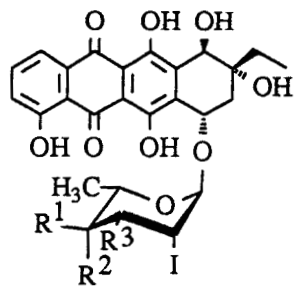
	R^1	R^2
8a,b	OAc	H
10a,b	H	OAc



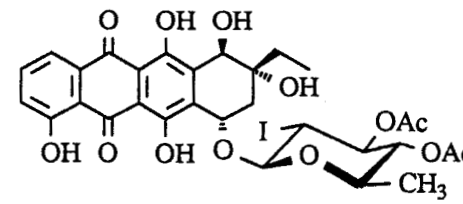
Dowex 50WX8 / MeOH

	R^1	R^2
9a,b	OAc	H
11a,b	H	OAc

Chromatography



	R^1	R^2	R^3
12	OAc	H	OAc
14	OH	H	OH
15	H	OAc	OAc
16	H	OH	OH



13

N-iodosuccinimide at a temperature of 0 - 10 °C. After 24 hours glycosides **8a,b**, and **9a,b** were obtained in 75% yield.

Although a complex mixture of four diastereoisomers (α- and β-anomer and *R*- and *S*-THP-ether) was obtained, the major reaction products were the α-(*R/S*)isomers. The α:β ratio was 7 : 1 as detected by NMR spectroscopy. A separation at this step was not necessary.

Without cleavage of the glycosidic linkage at position 7 the tetrahydropyranyl group at position 10 was hydrolyzed by treatment with acid ion exchange resin yielding the glycosides **12**, and **13**. These α- and β-glycosides were easily separated by column chromatography. By transesterification of **12** with sodium methoxide, the fully deblocked crystalline 2'-iodo-α-L-*manno*-glycoside **14** was obtained.

The glycosidation using 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (3,4-di-*O*-acetyl-L-fucal)[9] (**7**) again yielded the mixture of glycosides **10a,b** and **11a,b** in comparable amounts, also with an α : β ratio of 7 : 1 (deduced from the ^{1}H NMR data of the mixture). In this case the THP group was hydrolysed immediately and only the α-glycoside **15** was recovered by chromatography. When treated with sodium methoxide, compound **15** afforded the corresponding 2'-iodo-α-L-*talo*-glycoside **16**.

The analyses of the compounds by NMR spectroscopy at 300 and 400 MHz and by mass spectroscopy were in full agreement with the proposed structures.

EXPERIMENTAL

General Procedures. 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-3000 software. Specific rotations were determined 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 glycosidation reactions were performed under an argon cover in the presence of molecular sieve (3 Å). Preparative chromatography was performed on silica gel (Merck Kieselgel 60 particle size 0.015-0.040 mm) with the solvent systems specified.

10-*O*-Tetrahydropyranyl-β-rhodomycinone (5a,b). To a stirred solution of **3**[4] (840 mg, 1.78 mmol) and 3,4-dihydro-2*H*-pyran (3.4 mL, 37 mmol) in dry dichloromethane (60 mL) in the presence of molecular sieve (4 Å), was added a catalytic

amount of *p*-toluenesulfonic acid at room temperature. The mixture was stirred for 24 h. After filtration the organic phase was washed with saturated aqueous sodium hydrogen carbonate and water. The mixture was concentrated and codistilled with toluene for several times to yield the crude **7,9-*O*-phenylboronyl-10-*O*-tetrahydropyranyl-β-rhodomycinone (4a,b),** which was treated with 2-methyl-2,4-pentanediol (14 mL, 110 mmol) and molecular sieve (4 Å) in dry dichloromethane (50 mL) for 72 h at room temperature. Filtration, washing with saturated aqueous sodium hydrogen carbonate and water and drying (sodium sulfate) gave the crude mixture of compounds **5a,b**. The product was chromatographed on a column of silica gel (toluene-methanol 10:1) to give 720 mg (86%) of compound **5a,b**: mp 132-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3H, $J_{Me,CH}$ = 7.3 Hz, Me-14(a)), 1.03 (t, 3H, $J_{Me,CH}$ = 7.3 Hz, Me-14(b)), 1.75 (m 2H, CH_2-13(a,b)), 2.05 (dd, 2H, $J_{7,8a}$ = 2.0 Hz, $J_{8a,8b}$ = 14.0 Hz, H-8a(a,b)), 2.27 (dd, 2H, $J_{7,8b}$ = 5.5 Hz, $J_{8a,8b}$ = 14 Hz, H-8b(b)), 2.32 (dd, 2H, $J_{7,8b}$ = 5.5 Hz, $J_{8a,8b}$ = 14.0 Hz, H-8b(a)), 3.12-3.97 (m, 8H, CH_2-THP(a,b)), 4.81 (d, 1H, $J_{8a,10}$ = 1.1 Hz, H-10(a)), 4.91 (m, 1H, CH-THP(b)), 4.93 (d, 1H, $J_{8a,10}$ = 1.1 Hz, H-10(b)), 5.14 (dd, 1H, $J_{7,8a}$ = 2.0 Hz, $J_{7,8b}$ = 5.5 Hz, H-7(b)), 5.19 (dd, 1H, $J_{7,8a}$ = 2.0 Hz, $J_{7,8b}$ = 5.5 Hz, H-7(a)), 7.23 (dd, 1H, $J_{1,3}$ = 1.1 Hz, $J_{2,3}$ = 8.5 Hz, H-3(a,b)), 7.63 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.5 Hz, H-2(a,b)), 7.79 (dd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{1,3}$ = 1.1 Hz, H-1(a,b)), 11.96 (s, 1H, OH-4(a)), 11.97 (s, 1H, OH-4(b)), 12.81 (s, 1H, OH-6(a)), 12.82 (s, 1H, OH-6(b)), 13.60 (s, 1H, OH-11(a)), 13.66 (s, 1H, OH-11(b)). FAB - MS, m/z = 471 (M + H).

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-*manno*-hexopyranosyl)-10-*O*-tetrahydropyranyl-β-rhodomycinone (8a,b) and **7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-β-L-*gluco*-hexopyranosyl)-10-*O*-tetrahydropyranyl-β-rhodomycinone (9a,b).** To a solution of compound **5a,b** (420 mg, 0.9 mmol) in dry acetonitrile (30 mL) 3,4-di-*O*-acetyl-L-rhamnal (**6**) (320 mg, 1.5 mmol) and *N*-iodosuccinimide (280 mg, 1.25 mmol) were added at -10 °C. The mixture was stirred for 24 h, while the temperature was allowed to rise to room temperature. After filtration the mixture was diluted with dichloromethane and washed with aqueous sodium thiosulfate, aqueous sodium hydrogen carbonate and water and dried (sodium sulfate). Purified by chromatography (toluene-methanol 10:1), 540 mg (79%) of compounds **8a,b** and **9a,b** were obtained.

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-*manno*-hexopyranosyl)-β-rhodomycinone (12) and **7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-β-L-*gluco*-hexopyranosyl)-β-rhodomycinone (13).** Acid ion exchange resin Dowex 50 WX 8 (H^+) was added to a solution of compounds **8a,b** and **9a,b** (320 mg, 0.4 mmol) in dry methanol (10 mL) and the mixture was stirred for 24 h at room temperature. After the ion exchange resin had been filtered off, the two reaction products were separated by chromatography

(toluene-acetone 20:1). The first fraction was the β-glycoside **13**: 25 mg (9%), $[\alpha]_D^{25}$ +205° (c 0.02, chloroform), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, $J_{Me,CH}$ = 7.2 Hz, Me-14), 1.13 (d, 3H, $J_{5',6'}$= 6.5 Hz, Me-6'), 1.70 - 1.91 (m, 2H, CH_2-13), 2.02 (s, 3H, AcO), 2.08 (s, 3H, AcO), 2.10 (dd, 1H, $J_{7,8b}$ = 5.0 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8b), 2.48 (dd, 1H. $J_{7,8a}$ = 2.0 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8a), 3.64 (dq, 1H, $J_{4',5'}$ = 9.3 Hz, $J_{5',6'}$= 6.5 Hz, H-5'), 3.85 (dd, 1H, $J_{1',2'}$ = 9.1 Hz, $J_{2',3'}$ = 11.1 Hz, H-2'), 4.70 (dd, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 9.3 Hz, H-4'), 4.97 (s, 1H, H-10), 5.12 (d, 1H, $J_{1',2'}$ = 9.1 Hz, H-1'), 5.31 (dd, 1H, $J_{2',3'}$= 11.1 Hz, $J_{3',4'}$ = 9.3 Hz, H-3'), 5.44 (dd, 1H, $J_{7,8a}$ = 2.0 Hz, $J_{7,8b}$ = 5.0 Hz, H-7), 7.34 (dd, 1H, $J_{1,3}$ = 1.1 Hz, $J_{2,3}$ = 8.2 Hz, H-3), 7.73 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.2 Hz, H-2), 7.90 (dd, 1H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 1.1 Hz, H-1), 12.17 (s, 1H, OH-4), 12.98 (s, 1H, OH-6), 13.63 (s, 1H, OH-11). FAB - MS, m/z = 727 (M + H).

The second fraction was the α-glycoside **12**: 210 mg (66%), $[\alpha]_D^{25}$ +105° (c 0.02, chloroform), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, $J_{Me,CH}$ = 7.5 Hz, Me-14), 1.29 (d, 3H, $J_{5',6'}$= 6.3 Hz, Me-6'), 1.70 - 1.91 (m, 2H, CH_2-13), 2.01 (s, 3H, AcO), 2.04 (s, 3H, AcO), 2.11 (dd, 1H, $J_{7,8b}$ = 5.0 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8b), 2.22 (dd, 1H. $J_{7,8a}$ = 2.0 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8a), 2.8 (s, 1H, OH-10), 3.37 (s, 1H, OH-9), 4.04 (dq, 1H, $J_{4',5'}$ = 9.6 Hz, $J_{5',6'}$= 6.3 Hz, H-5'), 4.32 (dd, 1H, $J_{2',3'}$ = 4.4 Hz, $J_{3',4'}$ = 9.5 Hz, H-3'), 4.66 (dd, 1H, $J_{1',2'}$ = 1.1 Hz, $J_{2',3'}$ = 4.4 Hz, H-2'), 4.88 (s, 1H, H-10), 5.02 (dd, 1H, $J_{7,8a}$ = 2.0 Hz, $J_{7,8b}$ = 5.0 Hz, H-7), 5.18 (dd, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 9.5 Hz, H-4'), 5.71 (d, 1H, $J_{1',2'}$ = 1.1 Hz, H-1'), 7.28 (d, 1H, $J_{2,3}$ = 8 Hz, H-3), 7.69 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 8 Hz, H-2), 7.83 (d, 1H, $J_{1,2}$ = 8 Hz, H-1), 12.04 (s, 1H, OH-4), 12.79 (s, 1H, OH-6), 13.51 (s, 1H, OH-11). FAB - MS, m/z = 727 (M + H).

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-*talo*-hexopyranosyl)-β-rhodomycinone (15). Compound **5a,b** (206 mg, 0.44 mmol) was reacted with 3,4-di-*O*-acetyl-L-fucal (**7**) (170 mg, 0.8 mmol) and *N*-iodosuccinimide (150 mg, 0.66 mmol) and the product worked up analogously to compounds **8a,b** and **9a,b**. A crude mixture of **7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-*talo*-hexopyranosyl)-10-*O*-tetrahydropyranyl-β-rhodomycinone (10a,b)** and **7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-β-L-*galacto*-hexopyranosyl)-10-*O*-tetrahydropyranyl-β-rhodomycinone (11a,b)** was obtained in 73% yield (260 mg).

The THP-group was cleaved immediately by treating the mixture in methanol (15 mL) with Dowex 50 WX 8 (H^+) ion exchange resin for 24 h at room temperature. By chromatography (toluene-acetone 20:1) the α-glycoside **15** was eluted: 160 mg (69%), $[\alpha]_D^{25}$ +110° (c 0.01, chloroform), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, 3H, $J_{Me,CH}$ = 7.3 Hz, Me-14), 1.29 (d, 3H, $J_{5',6'}$= 6.5 Hz, Me-6'), 1.70 - 1.91 (m, 2H, CH_2-13), 2.02 (s, 3H, AcO), 2.24 (s, 3H, AcO), 2.18 (dd, 1H, $J_{7,8b}$ = 5.3 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8b), 2.22

(dd, 1H. $J_{7,8a}$ = 1.8 Hz, $J_{8a,8b}$ = 15.0 Hz, H-8a), 3.11 (s, 1H, OH-10), 3.37 (s, 1H, OH-9), 4.51 (m, 2H, H-5', H-2'), 4.74 (dd, 1H, $J_{2',3'}$ = 4.9 Hz, $J_{3',4'}$ = 3.6 Hz, H-3'), 4.81 (s, 1H, H-10), 5.05 (dd, 1H, $J_{7,8a}$ = 1.8 Hz, $J_{7,8b}$ = 5.3 Hz, H-7), 5.28 (d, 1H, $J_{3',4'}$ = 3.6 Hz, H-4'), 5.89 (s, 1H, H-1'), 7.22 (d, 1H, $J_{2,3}$ = 8 Hz, H-3), 7.64 (t, 1H, $J_{1,2} = J_{2,3}$ = 8 Hz, H-2), 7.78 (d, 1H, $J_{1,2}$ = 8 Hz, H-1), 11.89 (s, 1H, OH-4), 12.69 (s, 1H, OH-6), 13.36 (s, 1H, OH-11). FAB - MS, m/z = 727 (M + H).

7-*O*-(2,6-Dideoxy-2-iodo-α-L-*manno*-hexopyranosyl)-β-rhodomycinone (14). A solution of **12** (150 mg, 0.21 mmol) in methanol (5 mL) was treated with methanolic 0.1M sodium methoxide (0.2 mL) for 2 h at room temperature. Neutralization with Dowex 50 WX 8 (H^+) resin, filtration, concentration, and codistillation with toluene gave **14** (120 mg, 89 %), mp 133 °C, $[\alpha]_D^{25}$ +85° (c 0.02, chloroform : methanol 5 : 1), ^1H NMR (400 MHz, $CDCl_3$ + d_6DMSO 5 : 1) δ 1.08 (t, 3H, $J_{Me,CH}$ = 7.5 Hz, Me-14), 1.38 (d, 3H, $J_{5',6'}$= 6.2 Hz, Me-6'), 1.7 (m, 2H, CH_2-13), 3.46 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, H-4'), 3.97 (dq, 1H, $J_{4',5'}$ = 9.6 Hz, $J_{5',Me}$ = 6.3 Hz, H-5'), 4.45 (dd, 1H, $J_{1',2'}$ = 1.1 Hz, $J_{2',3'}$ = 4.4 Hz, H-2'), 4.81 (s, 1H, H-10), 5.07 (dd, 1H, $J_{7,8a}$ = 2.0 Hz, $J_{7,8b}$ = 5.0 Hz, H-7), 5.71 (d, 1H, $J_{1',2'}$ = 1.1 Hz, H-1'), 7.35 (dd, 1H, $J_{1,3}$ = 1.1 Hz, $J_{2,3}$ = 8.4 Hz, H-3), 7.76 (t, 1H, $J_{1,2} = J_{2,3}$ = 8.4 Hz, H-2), 7.91 (dd, 1H, $J_{1,3}$ = 1.1 Hz, $J_{1,2}$ = 8.4 Hz, H-1), 12.18 (s, 1H, OH-4), 12.93 (s, 1H, OH-6), 13.72 (s, 1H, OH-11). FAB - MS, m/z = 649 (M + Li).

7-*O*-(2,6-Dideoxy-2-iodo-α-L-*talo*-hexopyranosyl)-β-rhodomycinone (16). A solution of **15** (30 mg, 0.04 mmol) in methanol (2 mL) was treated with methanolic 0.1M sodium methoxide (0.05 mL) for 2 h at room temperature. Neutralization with Dowex 50 WX 8 (H^+) resin, filtration, concentration, and codestillation with toluene gave **16** (25 mg, 94 %), mp 95 °C, $[\alpha]_D^{25}$ +90° (c 0.021, chloroform : methanol 5 : 1), ^1H NMR (300 MHz, $CDCl_3$ + d_6DMSO 5 : 1) δ 1.04 (t, 3H, $J_{Me,CH}$ = 7.6 Hz, Me-14), 1.33 (d, 3H, $J_{5',6'}$= 6.5 Hz, Me-6'), 1.72 (m, 2H, CH_2-13), 3.75 (m, 2H, H-3', H-4'), 4.20 (q, 1H, $J_{5',6'}$= 6.5 Hz, H-5'), 4.28 (s, 1H, H-2'), 4.79 (s, 1H, H-10), 5.03 (s, 1H, H-7), 5.84 (s, 1H, H-1'), 7.25 (d, 1H, $J_{2,3}$ = 7.5 Hz, H-3), 7.65 (t, 1H, $J_{1,2} = J_{2,3}$ = 7.5 Hz, H-2), 7.78 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 12.02 (s, 1H, OH-4), 12.78 (s, 1H, OH-6), 13.51 (s, 1H, OH-11). FAB - MS, m/z = 649 (M + Li).

ACKNOWLEDGEMENT

The authors would like to thank Dr. S. Berger of the University of Marburg for measuring the ^1H NMR spectra and Dr. H.-W. Fehlhaber, Hoechst AG, Frankfurt for performing the MS analysis.

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