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Semisynthetic ε-(iso)rhodomycins: a new glycosylation variant and modification reactions

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ABSTRACT

Synthesis of 7-*O*-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-ε-(iso)rhodomycinones **16** and **17**, and their 3'-morpholino derivatives are described. Glycosylation (trimethylsilyl triflate, 10:1 dichloromethane–acetone, −35°) of 1-*O*-*tert*-butyldimethylsilyl-2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranose (**4**) with ε-rhodomycinone (ε-RMN, **5**) or ε-isorhodomycinone (ε-isoRMN, **6**) afforded 7-*O*-α-glycosyl-ε-RMN (**9**) and -ε-isoRMN (**12**) in high yield. The glycosyl donors 2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*lyxo*-hexopyranose (**2**) or its 1-*O*-trimethylsilylated α-anomer **3** were less suitable for the glycosylation of these aglycons. Saponification of **9** and **12** provided **16** and **17**, respectively, which reacted with various 2,2'-oxydiacetaldehydes under conditions of reductive alkylation to give 3'-morpholinyl-ε-(iso)rhodomycins.

INTRODUCTION

In a quest for semisynthetic anthracyclines which should be effective as antitumor agents, our synthesis project has focused on ε-rhodomycins and their 1-hydroxy analogues, the ε-isorhodomycins[1,2].

The main problems in the preparation of semisynthetic ε-(iso)rhodomycins are the scale-up chromatography of the microbial aglycons[3] and their glycosylation with functionalised 2,3,6-trideoxy-3-trifluoroacetamido-L-*lyxo*-hexopyranosyl donors[1,2,4]. Separation of ε-rhodomycinone (**5**, ε-RMN) and ε-isorhodomycinone (**6**, ε-isoRMN) (both obtained from a strain of *Streptomyces purpurascens*) is troublesome due to their poor solubility and similar chromatographic mobilities[4]. Glycosylation of **5** or **6** requires the use of 2.5–4 equiv. of 2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*lyxo*-hexopyranosyl chloride[4] or *p*-nitrobenzoate[1,5]. The use of the corresponding glycal in the condensation step yields mono- and di-glycosylated products[2].

One approach to new pharmacologically active anthracyclines is the synthesis of morpholino analogues[6]. Reductive *N*-alkylation of the anthracyclines with a dialdehyde in the presence of sodium cyanoborohydride is a versatile, one-step method for making such structural changes.

We now report a new method for the glycosylation of ε-(iso)rhodomycinones using 1-*O*-trialkylsilyl-L-*lyxo*-hexopyranose derivatives and modification of 7-*O*-glycosyl-ε-(iso)rhodomycinones by attachment of a chiral morpholinyl ring to the sugar moiety.

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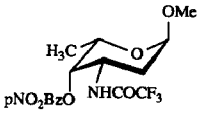
RESULTS AND DISCUSSION

Separation of ε-RMN[7] (**5**) and ε-isoRMN[8] (**6**), first described by Brockmann *et al.*[3], was achieved in two steps. Chromatography of the crude fermentation mixture on silica gel afforded a fraction that contained **5** and **6**, and chromatography on cellulose gave **5** or **6** with >96% purity.

In order to improve the accessibility of the 7-*O*-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-ε-(iso)rhodomycinones **16** (ref. 4) and **17** (ref. 2), the use of new glycosyl donors was investigated. First, 2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*lyxo*-hexopyranose (**2**), obtained from the methyl glycoside **1** (ref. 9) by treatment with aqueous 30% trifluoroacetic acid, was reacted with **5**. Condensation (Me_3Si triflate, triethylamine, dichloromethane, −15°) of **2** with **5** afforded a complex mixture from which 56% of the desired α-glycoside **9** was isolated. Since t.l.c. indicated that **2** was silylated[10] during the glycosylation, the 1-*O*-trimethylsilyl derivative **3** was synthesised and used as the glycosyl donor. The synthesis of glycosyloxytrimethylsilanes and their use for the preparation of α,α- and α,β-trehaloses[11–13] and related disaccharides[14–16] or aryl glycosides[17] have been described but, to our knowledge, structures related to **3** have not been reported. The α-anomer **3**, stereoselectively obtained by the reaction of **2** with chlorotrimethylsilane in 1:1 dichloromethane–pyridine at 0°, was condensed (Me_3Si triflate, molecular sieves 4 Å, 10:1 dichloromethane–acetone, −35°) with **5**, to afford **9** (32%) and a complex mixture of by-products. Column chromatography of this mixture on silica gel gave the daunosamine derivatives **2** and **3**, ε-RMN (**5**), 7-*O*-trimethylsilyl-ε-RMN (**7**), 7-*O*-α- (**9**) and -β-glycosyl-ε-RMN (**11**), 7,9-bis-*O*-(α-glycosyl)-ε-RMN (**10**), and the 1,1′-*O*-α,α- (**14**) and -α,β-linked disaccharide[18] (**15**). During processing, **5** was silylated to give **7** first, followed, after desilylation of **3**, by the main products **9**, **14**, and **15**. The structure of the by-products was proved by ^{1}H-n.m.r. spectroscopy, ^{1}H,^{1}H-COSY experiments, or f.a.b.-mass spectrometry. Additionally, the structure of **7** was confirmed by trimethylsilylation of **5**.



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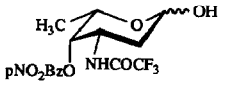

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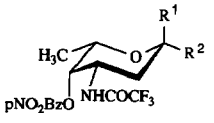
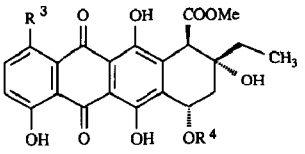


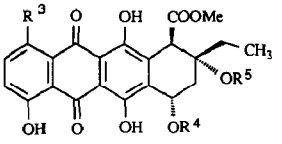
3 $R^1 = Me_3SiO$, $R^2 = H$

4 $R^1 = H$, $R^2 = {}^tBuMe_2SiO$

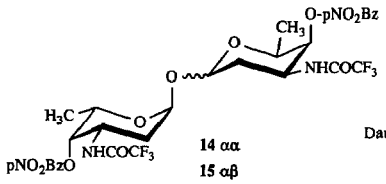
Because of the limited stability of **3** in the glycosylation reaction, the trimethylsilyl group was replaced by a *tert*-butyldimethylsilyl group[19–21]. Condensation of the β-anomer **4**, obtained by *tert*-butyldimethylsilylation[20] of **2**, with **5**, under the conditions described above, afforded 82% of the desired α-glycoside **9** together with 5% of the diglycoside **10**. Similarly, condensation of **4** and **6** gave the monoglycoside **12** (74%) and diglycoside **13** (5%). During these reactions, the aglycons were temporarily silylated



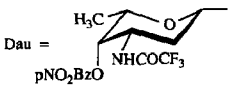
5 $R^3 = R^4 = H$
6 $R^3 = OH, R^4 = H$
7 $R^3 = H, R^4 = Me_3Si$
8 $R^3 = OH, R^4 = Me_3Si$



9 $R^3 = R^5 = H, R^4 = \alpha Dau$
10 $R^3 = H\ R^4 = R^5 = \alpha Dau$
11 $R^3 = R^5 = H, R^4 = \beta Dau$
12 $R^3 = OH, R^4 = \alpha Dau, R^5 = H$
13 $R^3 = OH, R^4 = R^5 = \alpha Dau$



14 αα
15 αβ



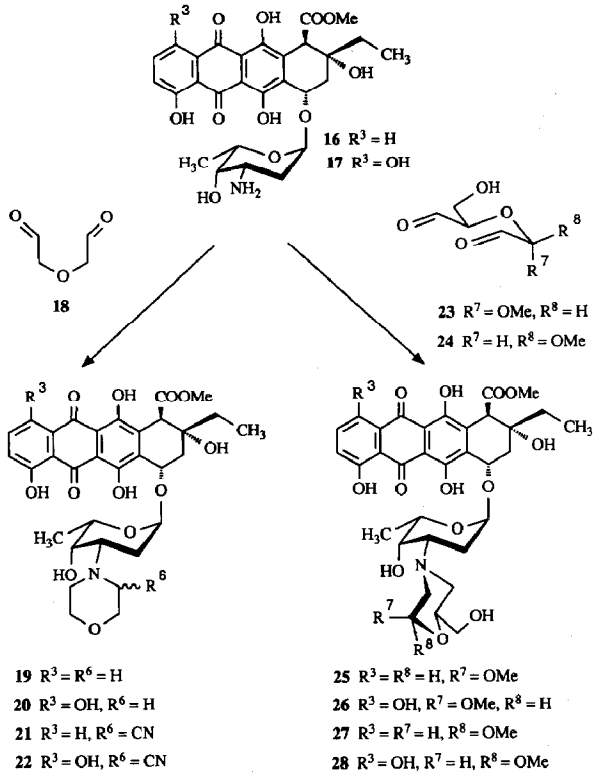
and **7** or **8** was detected by t.l.c. Use of *tert*-butyldimethylsilyl triflate as the glycosylation promoter instead of trimethylsilyl triflate avoided silylation of the aglycons, but condensation occurred more slowly.

Saponification[1,2] (M NaOH) of **9** and **12** afforded 7-*O*-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-ε-RMN (**16**) and -ε-isoRMN (**17**), respectively.

Further modification[22,23] of **16** and **17**, especially the introduction[24] of a morpholino ring at C-3′, could improve the antitumor efficacy of ε-(iso)rhodomycins. For comparative purposes, the 3′-morpholinyl-ε-(iso)rhodomycins **19** and **20** were prepared. Treatment[24] (sodium cyanoborohydride, MeOH, pH 9) of **16** or **17** with 2,2′-oxydiacetaldehyde (**18**) afforded **19** and **20**, and their 3″-cyano derivatives **21** and **22**. The formation of **21** and **22** can be avoided[25] if the reaction is carried out at pH 3.

The dialdehydes[26] **23** and **24**, obtained by oxidation (0.1M $NaIO_4$) of methyl α- or β-D-galactopyranoside, were used in order to obtain morpholino derivatives with chiral centres at C-2 and C-6. Reductive alkylation (sodium cyanoborohydride, MeOH, pH 3) of **16** or **17** with **23** gave the 6″(*S*)-hydroxymethyl-2″(*S*)-methoxymorpholino derivatives **25** and **26**, respectively, and with **24** the 6″(*S*)-hydroxymethyl-2″(*R*)-methoxymorpholino derivatives **27** and **28**, respectively, without formation of the cyanomorpholino by-products. $^1H,^1H$-COSY experiments were used to assign the resonances of the sugar and aglycon A-ring protons in the ^1H-n.m.r. spectra of **25**–**28**. In each compound, the *lyxo*-hexopyranose moiety and the morpholino rings are in the $^1C_4$ and $^5C_2$ conformations, respectively.

Compounds **25** and **26**, which exhibited a similar activity to doxorubicin in *in vitro* and *in vivo* (L1210 mouse leukemia) tests for cytotoxicity, were selected for further oncopharmacological evaluation.



EXPERIMENTAL

General. — Reactions were carried out at ambient temperature unless otherwise stated. Solutions were concentrated under reduced pressure at $<40°$ (bath). Organic solutions were washed with 0.1M potassium dihydrogen phosphate or 0.1M sodium citrate adjusted to the appropriate pH value using 0.1M NaOH or 0.1M HCl. Melting points, determined on a Büchi apparatus, are uncorrected. ^{1}H-N.m.r. spectra were recorded with a Bruker AC-200, AC-300, or Jeol GX-400 spectrometer, on solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. 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 optical rotations were determined with a Perkin–Elmer 241 polarimeter equipped with 10-cm cuvettes, for solutions in $CHCl_3$ at 24°, unless noted otherwise. Reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck) with detection by u.v. light or by charring with sulphuric acid. Preparative chromatography was performed on Kieselgel 60 (Merck, 0.015–0.040 mm). The glycosylations were performed under argon or nitrogen.

2,2'-Oxydiacetaldehydes **23** *and* **24**. — To a solution of methyl α- or β-D-galactopyranoside (5.0 g, 25.75 mmol) in ethanol (100 mL) was added dropwise 0.1M sodium periodate (500 mL). After stirring for 3 h at room temperature, the mixture was concentrated *in vacuo*. A solution of the residue in 10:1 ethyl acetate–methanol (150 mL)

was stirred with Na_2SO_4 (7.5 g) for 15 min and filtered, and the insoluble material was washed with ethyl acetate (100 mL). The combined filtrate and washings were concentrated *in vacuo* to give crude **23** or **24** (4.15 g), which was used without further purification.

Morpholino derivatives. — To a solution of aminoglycoside (1.07 mmol) in methanol (100 mL, adjusted to pH 3 with acetic acid) were added a solution of dialdehyde (2.20 mmol) in methanol (25 mL) and sodium cyanoborohydride (0.296 g, 4.7 mmol). After stirring for 24 h, the mixture was concentrated *in vacuo*. Column chromatography (95:5:1:0.25:0.1 chloroform–methanol–acetic acid–water–triethylamine) of the residue on silica gel (100 g) and on aminated silica gel (120 g, LiChroprep NH2, 25–40 μm, Merck) with 9:1 chloroform–methanol afforded the morpholino derivative.

*2,3,6-Trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-*α-L-lyxo-*hexopyranose* (**2**). — A solution of methyl 2,3,6-trideoxy-4-*O-p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside[9] (**1**; 25.0 g, 61.5 mmol) in aqueous 30% trifluoroacetic acid (250 mL) was heated under reflux for 10 min, then cooled, and extracted with ethyl acetate (300 ml × 3), and the combined extracts were washed with M phosphate buffer (pH 7.0, 200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Crystallisation of the residue from ether gave **2** (14.9 g, 62%). Column chromatography (9:1 chloroform–ethyl acetate) of the remaining oil (6 g) on silica gel (100 g) yielded more (2.5 g) **2**, m.p. 213°, $[\alpha]_D$ −192° (*c* 0.86, ethyl acetate), R_F 0.21. ^{1}H-N.m.r. data (300 MHz): δ 8.36–8.26 (m, 4 H, aromatic), 6.42 (d, 1 H, $J_{3,NH}$ 8.2 Hz, NH-3), 5.47 (bs, 1 H, H-4), 5.39 (bs, 1 H, H-1), 4.67 (m, 1 H, H-3), 4.35 (q, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 2.05 (ddd, 1 H, $J_{1,2ax}$ 3.5, $J_{2ax,3}$ 12.3, $J_{2ax,2eq}$ 12.3 Hz, H-2ax), 1.84 (dd, 1 H, $J_{2eq,3}$ 4.3 Hz, H-2eq), 1.13 (d, 1 H, H-6,6,6).

Anal. Calc. for $C_{15}H_{15}F_3N_2O_7$ (392.29): C, 45.93; H, 3.85; N 7.14. Found: C, 45.87; H, 3.89; N 7.03.

*2,3,6-Trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-1-O-trimethylsilyl-*α-L-lyxo-*hexopyranose* (**3**). — To a solution of **2** (4.60 g, 11.72 mmol) in 1:1 dichloromethane–pyridine (80 mL) was added chlorotrimethylsilane (4.46 mL) at 0°. The mixture was stirred for 12 h at 0°, then diluted with dichloromethane (100 mL), washed with phosphate buffer (pH 7.5, 200 mL × 2), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (10:10:1 dichloromethane–light petroleum–acetone) of the residue on silica gel (100 g) gave **3** (5.08 g, 93.3%), m.p. 134°, $[\alpha]_D$ −174° (*c* 0.49), R_F 0.66. ^{1}H-N.m.r. data (300 MHz): δ 8.33–8.23 (m, 4 H, aromatic), 6.35 (d, 1 H, $J_{3,NH}$ 7.5 Hz, NH), 5.47 (bs, 1 H, H-1), 5.44 (bs, 1 H, H-4), 4.77 (m, 1 H, H-3), 4.25 (q, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 2.05 (ddd, 1 H, $J_{1,2ax}$ 3.0, $J_{2ax,3}$ 12.0, $J_{2ax,2eq}$ 12.5 Hz, H-2ax), 1.91 (ddt, 1 H, $J_{1,2eq}$ 1.2, $J_{2eq,3}$ 4.5, $J_{2eq,4}$ 1.2 Hz, H-2eq), 1.15 (d, 3 H, H-6,6,6), 0.25 (s, 9 H, $SiMe_3$).

Anal. Calc. for $C_{18}H_{23}F_3N_2O_7Si$ (464.47): C, 46.55; H, 4.99; N, 6.03. Found: C, 46.46; H, 4.98; N, 5.93.

*1-*O-tert-*Butyldimethylsilyl-2,3,6-trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-β-L-lyxo-hexopyranose* (**4**). — To a stirred solution of **2** (8.10 g, 20.6 mmol) in 1:1 1,2-dichloroethane–pyridine (320 mL) was added *tert*-butylchlorodimethylsilane (15.4 g, 103 mmol). After heating under reflux for 24 h, the mixture was cooled, diluted with

1,2-dichloroethane, washed with 0.1M phosphate buffer (pH 7.5, 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Toluene (200 mL) was evaporated from the residue, column chromatography (10:10:1 chloroform–light petroleum-acetone) of which on silica gel (250 g) then gave **4** (9.44 g, 90.3%), m.p. 72–74°, $[\alpha]_D$ −91° (*c* 1), R_F 0.43. ^{1}H-N.m.r. data (200 MHz): δ 8.36–8.25 (m, 4 H, aromatic), 6.40 (d, 1 H, $J_{3,NH}$ 7.5 Hz, NH), 5.34 (bs, 1 H, H-4), 4.94 (dd, 1 H, $J_{1,2ax}$ 7.7, $J_{1,1eq}$ 2.0 Hz, H-1), 4.37 (m, 1 H, H-3), 3.85 (dq, 1 H, $J_{4,5}$ 1.0, $J_{5,6}$ 6.5 Hz, H-5), 2.08 (ddd, 1 H, $J_{2eq,3}$ 4.5, $J_{2ax,2eq}$ 12.3 Hz, H-2eq), 1.84 (ddd, 1 H, $J_{2ax,3}$ 12.2 Hz, H-2ax), 1.24 (d, 3 H, H-6,6,6), 0.94 (s, 9 H, $SiCMe_3$), 0.18 and 0.16 (2 s, 6 H, $SiMe_2$).

Anal. Calc. for $C_{21}H_{29}F_3N_2O_7Si$ (506.56): C, 49.79; H, 5.77; N, 5.53; Si, 5.54. Found: C, 49.81; H, 5.78; N, 5.45.

ε-Rhodomycinone (**5**) *and ε-isorhodomycinone* (**6**). — Column chromatography (44:5:1 dichloromethane–methanol–formic acid) of a crude fermentation mixture[7] (17.0 g, containing 21.3% of ε-RMN and 41.8% of ε-isoRMN) on silica gel (400 g) gave a mixture (13.1 g) of **5** and **6**. A solution of the mixture in chloroform (500 mL) was stirred with cellulose (66.0 g) for 10 min. The suspension was concentrated *in vacuo*, and the residue was pulverised, applied to a column of cellulose (130 g), and eluted in sequence with 2:1 and 1:1 light petroleum–dichloromethane and 1:1 dichloromethane–acetone to give three fractions, which, after concentration *in vacuo*, afforded **5** (2.0 g, containing 96% of **5** and <1% of **6**), **5** and **6** (2.5 g, containing 20% of **5** and 80% of **6**), and **6** (8.0 g, containing <1% of **5** and 97% of **6**). Compound **5** had m.p. 216–218°, $[\alpha]_D$ +89° (*c* 0.03), R_F 0.41 (95:5:1:0.25:0.1 chloroform–acetone–acetic acid–water–triethylamine); lit.[7] m.p. 210°. Compound **6** had m.p. 226–228°; lit.[8] m.p. 227–229°.

7-O-Trimethylsilyl-ε-rhodomycinone (**7**). — To a solution of **5** (200 mg, 0.46 mmol) in 1:1 dichloromethane–pyridine (10 mL) was added chlorotrimethylsilane (0.18 mL) at 0°. After stirring for 16 h at 0°, the mixture was diluted with dichloromethane (20 mL), washed with phosphate buffer (pH 7.5, 15 mL × 3), dried ($MgSO_4$), and concentrated *in vacuo*. Toluene (20 mL × 3) was evaporated from the residue, column chromatography (200:1 chloroform–triethylamine) of which on silica gel (15 g) then gave **7** (174 mg, 76%), m.p. 191°, $[\alpha]_D$ +279° (*c* 0.04). ^{1}H-N.m.r. data (200 MHz): δ 13.48, 12.80, and 12.22 (3 s, 3 H, HO-4,6,11), 7.77 (dd, 1 H, $J_{1,2}$ 7.5, $J_{1,3}$ 1.2 Hz, H-1), 7.60 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-2), 7.22 (dd, 1 H, H-3), 5.37 (dd, 1 H, ΣJ 6.0 Hz, H-7) 5.13 (s, 1 H, HO-9), 4.24 (s, 1 H, H-10), 3.63 (s, 3 H, COOMe), 2.13 (dd, 1 H, $J_{7,8A}$ 3.8, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.04 (dd, 1 H, $J_{7,8B}$ 2.2 Hz, H-8B), 1.72 (m, 1 H, $J_{13A,14}$ 7.2, $J_{13A,13B}$ 13.9 Hz, H-13A), 1.37 (m, 1 H, H-13B), 1.05 (t, 3 H, H-14,14,14), 0.21 (s, 9 H, $SiMe_3$).

Anal. Calc. for $C_{25}H_{28}O_9Si$ (500.58): C, 59.99; H, 5.64; Found: C, 60.23; H, 5.71.

7-O-Trimethylsilyl-ε-isorhodomycinone (**8**). — Treatment of **6** (200 g, 0.45 mmol) with chlorotrimethylsilane, as described for **7**, gave, after column chromatography (200:1 chloroform-triethylamine), **8** (172 mg, 76%), m.p. 140° (dec. 240°), $[\alpha]_D$ +326° (*c* 0.006). ^{1}H-N.m.r. data (200 MHz): δ 12.92, 12.80, 12.32, and 12.23 (4 s, 4 H, HO-1,4,6,11), 7.22 (bs, 2 H, H-2,3), 5.37 (dd, 1 H, $J_{7,8A}$ 3.8, $J_{7,8B}$ 2.0 Hz, H-7), 5.15 (bs, 1 H, HO-9), 4.24 (s, 1 H, H-10), 3.64 (s, 3 H, COOMe), 2.12 (dd, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.05 (dd, 1 H, H-8B), 1.72 (m, 1 H, $J_{13A,14}$ 7.3, $J_{13A,13B}$ 14.0 Hz, H-13A), 1.38 (m, 1 H,

H-13B), 1.05 (t, 3 H, H-14,14,14), 0.20 (s, 9 H, $SiMe_3$).

Anal. Calc. for $C_{25}H_{28}O_{10}Si$ (516.58): C, 58.13; H, 5.46. Found: C, 58.19; H, 5.49.

Glycosylation of ε-RMN (**5**) *using the 1-O-trimethylsilyl donor* **3**. — To a mixture of **5** (300 mg, 0.70 mmol), **3** (324 mg, 0.64 mmol), and powdered molecular sieves 4 Å (800 mg) in 10:1 dichloromethane–acetone (25 mL) was added Me_3Si triflate (0.13 mL) at −35°. After stirring for 2 h and further addition of a solution of **3** (155 mg, 0.33 mmol) in dichloromethane (10 mL) and Me_3Si triflate (0.12 mL), the mixture was stirred for 16 h at −35°, neutralised with triethylamine (0.5 mL), diluted with dichloromethane (25 mL), filtered, washed with 0.1M citrate buffer (15 mL × 3, pH 5.5) and ice–water (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (95:5:1:0.25:0.1 chloroform–acetone–acetic acid–water–triethylamine) of the residue on silica gel (25 g) gave **2** (50 mg, 19%), **3** (40 mg, 9.2%), **5** (90 mg, 30%), **7** (30 mg, 8.5%), **9** (180 mg, 32%), **10** (20 mg, 2.4%), **11** (50 mg, 8.9%), **14** (70 mg, 28.4%), and **15** (70 mg, 28.4%).

7-*O*-(2,3,6-Trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-ε-rhodomycinone (**9**) had m.p. 211°, $[\alpha]_D$ −31° (*c* 0.07); R_F 0.56; lit.[4] reported as an intermediate. ^{1}H-N.m.r. data (300 MHz): δ 13.49, 12.93, and 12.11, (3 s, 3 H, HO-4,6,11), 8.26–8.26 (m, 4 H, aromatic), 7.88 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 7.71 (dd, 1 H, $J_{2,3}$ 8.2 Hz, H-2), 7.32 (d, 1 H, H-3), 6.26 (d, 1 H, $J_{3',NH}$ 7.2 Hz, NH-3′), 5.66 (s, 1 H, H-1′), 5.48 (d, 1 H, $J_{3',4'}$ 1.5 Hz, H-4′), 5.29 (bs, 1 H, H-7), 4.49 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5′), 4.46 (m, 1 H, H-3′), 4.34 (s, 1 H, H-10), 3.94 (bs, 1 H, HO-9), 3.74 (s, 3 H, COOMe), 2.38 (ddd, 1 H, $J_{7,8A}$ 2.0, $J_{8A,10}$ 1.0, $J_{8A,8B}$ 15.2 Hz, H-8A), 2.30 (dd, 1 H, $J_{7,8B}$ 3.8 Hz, H-8B), 2.15 (dd, 1 H, $J_{2'eq,3'}$ 4.5, $J_{2'ax,2'eq}$ 13.0 Hz, H-2′eq), 2.09 (ddd, 1 H, $J_{1',2'ax}$ 3.2, $J_{2'ax,3'}$ 12.2 Hz, H-2′ax), 1.87 (m, 1 H, $J_{13A,14}$ 7.2, $J_{13A,13B}$ 15 Hz, H-13A), 1.48 (m, 1 H, H-13B), 1.27 (d, 3 H, H-6′,6′,6′), 1.17 (t, 3 H, H-14,14,14).

Anal. Calc. for $C_{37}H_{33}F_3N_2O_{15}$ (802.68): C, 55.37; H, 4.14; N, 3.49. Found: C, 55.45; H, 4.18; N, 3.41.

7,9-Bis-*O*-(2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-ε-rhodomycinone (**10**) had m.p. 183–185°, $[\alpha]_D$ −16° (*c* 0.1), R_F 0.59. ^{1}H-N.m.r. data (400 MHz): δ 13.61, 13.02, and 12.19 (3 s, 3 H, HO-4,6,11), 8.29 and 8.23 (dt, 4 H, aromatic), 7.88 (dd, 1 H, $J_{1,2}$ 7.5, $J_{1,3}$ 1.0 Hz, H-1), 7.71 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-2), 7.40 (d, 1 H, $J_{3'',NH}$ 5.7 Hz, NH-3″), 7.33 (dd, 1 H, H-3), 6.99 (d, 1 H, $J_{3',NH}$ 7.6 Hz, NH-3′), 5.64 (d, 1 H, $J_{1'',2''ax}$ 3.5 Hz, H-1″), 5.47 (d, 1 H, $J_{1',2'ax}$ 2.6 Hz, H-1′), 5.42 (bs, 1 H, H-4′), 5.23 (bs, 1 H, H-4″), 5.08 (d, 1 H, $J_{7,8B}$ 5.5 Hz, H-7), 4.86 (d, 1 H, $J_{8A,10}$ 1.2 Hz, H-10), 4.71 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5′), 4.60 and 4.58 (m, 2 H, H-3′,3″), 3.80 (q, 1 H, $J_{5'',6''}$ 6.5 Hz, H-5″), 3.73 (s, 3 H, COOMe), 2.58 (ddd, 1 H, $J_{7,8A}$ 1.0 Hz, H-8A), 2.31 (m, 1 H, $J_{13A,14}$ 7.5, $J_{13A,13B}$ 15.0 Hz, H-13A), 2.25 (dd, 1 H, $J_{2''eq,3''}$ 3.8, $J_{2''ax,2''eq}$ 12.5 Hz, H-2″eq), 2.21 (dd, 1 H, H-8B), 2.09 (dd, 1 H, $J_{2'eq,3'}$ 3.6, $J_{2'ax2'eq}$ 11.0 Hz, H-2′eq), 2.04 (m, 2 H, H-2′ax,2″ax), 1.36 (d, 3 H, H-6′,6′,6′), 1.06 (t, 3 H, $J_{13A,14}$ H-14,14,14), 0.61 (d, 3 H, H-6″,6″,6″).

Anal. Calc. for $C_{52}H_{46}F_6N_4O_{21}$ (1176.95): C, 53.07; H, 3.94; N, 4.76. Found: C, 53.19; H, 3.95; N, 4.66.

7-*O*-(2,3,6-Trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-β-L-*lyxo*-hexo-

pyranosyl)-ε-rhodomycinone (**11**) had m.p. 155–158°, $[\alpha]_D$ +228° (*c* 0.13), R_F 0.47. ^{1}H-N.m.r. data (300 MHz); δ 13.52, 13.02, and 13.12 (3 s, 3 H, HO-4,6,11), 8.29–8.24 (m, 4 H, aromatic), 7.86 (dd, 1 H, $J_{1,2}$ 7.5, $J_{1,3}$ 1.1 Hz, H-1), 7.70 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-2), 7.31 (dd, 1 H, H-3), 6.62 (d, 1 H, $J_{3',NH}$ 7.7 Hz, NH), 5.65 (dd, 1 H, $J_{7,8A}$ 1.5, $J_{7,8B}$ 3.5 Hz, H-7), 5.37 (d, 1 H, $J_{3',4'}$ 2.5 Hz, H-4'), 5.19 (dd, 1 H, $J_{1',2'ax}$ 9.3, $J_{1',2'eq}$ 2.0 Hz, H-1'), 4.52 (s, 1 H, HO-9), 4.46 (m, 1 H, H-3'), 4.39 (s, 1 H, H-10), 3.90 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5'), 3.37 (s, 3 H, COOMe), 2.42 (d, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.20 (dd, 1 H, H-8B), 2.20 (dd, 1 H, H-2'eq), 1.98 (ddd, 1 H, $J_{2'ax,3'}$ 12.5, $J_{2'ax,2'eq}$ 13.0 Hz, H-2'ax), 1.80 (m, 1 H, $J_{13A,14}$ 7.2, $J_{13A,13B}$ 15.0 Hz, H-13A), 1.50 (m, 1 H, H-13B), 1.17 (d, 3 H, H-6',6',6'), 1.15 (t, 3 H, H-14,14,14).

Anal. Calc. for $C_{37}H_{33}F_3N_2O_{15}$ (802.68): C, 55.37; H, 4.14; N, 3.49. Found: C, 55.46; H, 4.17; N, 3.42.

2,3,6-Trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl 2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**14**) had m.p. 155–160°, $[\alpha]_D$ −160° (*c* 0.49), R_F 0.28. ^{1}H-N.m.r. data (200 MHz): δ 8.23–8.33 (m, 8 H, aromatic), 6.62 (d, 2 H, $J_{3,NH}$ 7.5 Hz, NH-3,3'), 5.50 (bs, 2 H, H-4,4'), 5.44 (bs, 2 H, H-1,1'), 4.72 (m, 2 H, H-3,3'), 4.23 (q, 2 H, $J_{5,6}$ 6.5 Hz, H-5,5'), 2.23 (ddd, 2 H, $J_{1,2ax} = J_{1',2'ax} = 3.5$, $J_{2ax,3} = J_{2'ax,3'} = 12.0$, $J_{2ax,2eq} = J_{2'ax,2'eq} = 12.4$ Hz, H-2ax,2'ax), 2.03 (dd, 2 H, $J_{2eq,3} = J_{2'eq,3'} = 4.5$ Hz, H-2eq,2'eq), 1.22 (d, 6 H, H-6,6,6,6',6',6'). F.a.b.-mass spectrum: *m/z* 767 ($M + H^+$), 375 (glycosyl$^+$).

Anal. Calc. for $C_{30}H_{28}F_6N_4O_{13}$ (766.57): C, 47.01; H, 3.68; N, 7.31. Found: C, 47.20; H, 3.69; N, 7.24.

2,3,6-Trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranosyl 2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**15**) had m.p. 147–149°, $[\alpha]_D$ −127° (*c* 0.32), R_F 0.23. ^{1}H-N.m.r. data (200 MHz): δ 8.20–8.33 (m, 8 H, aromatic), 6.60 and 6.47 (d, 2 H, $J_{3,NH} = J_{3',NH} = 7.0$ Hz, NH-3,3'), 5.48 (bs, 1 H, H-1'), 5.37 (bs, 2 H, H-4,4'), 4.89 (dd, 1 H, $J_{1,2ax}$ 8.9, $J_{1,2eq}$ 2.0 Hz, H-1), 4.85 (m, 1 H, H-3), 4.63 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5'), 4.42 (m, 1 H, H-3'), 3.91 (q, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 2.15–2.05 (m, 3 H, H-2eq,2'eq,2'ax), 1.93 (ddd, 1 H, $J_{2ax,3}$ 12.5, $J_{2ax,2eq}$ 12.5 Hz, H-2ax), 1.27 and 1.17 (d, 6 H, H-6,6,6,6',6',6').

Anal. Calc. for $C_{30}H_{28}F_6N_4O_{13}$ (766.57): C, 47.01; H, 3.68; N, 7.31. Found: C, 47.14; H, 3.71; N, 7.23.

*7-*O*-(2,3,6-Trideoxy-4-*O*-p-nitrobenzoyl-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)-ε-rhodomycinone* (**9**). — To a stirred mixture of **5** (5.40 g, 12.60 mmol), **4** (8.30 g, 16.38 mmol), and molecular sieves 4 Å (5.0 g) in 10:1 dichloromethane–acetone at −35° was added Me_3Si triflate (3.3 mL). After the mixture had been stirred for 16 h at −35°, triethylamine (4.6 mL) was added, and the mixture was filtered, washed with water (250 mL) and phosphate buffer (pH 8, 200 mL × 2), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (95:5:1:0.25:0.1 chloroform–acetone–acetic acid–water–triethylamine) of the residue (14.7 g) on silica gel (1000 g) gave **9** (8.32 g, 82.3%) and 7,9-diglycoside **10** (0.63 g, 4.2%).

*7-*O*-(2,3,6-Trideoxy-4-*O*-p-nitrobenzoyl-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)-ε-isorhodomycinone* (**12**) *and 7,9-bis-*O*-(2,3,6-trideoxy-4-*O*-p-nitrobenzoyl-3-*

*trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)-ε-isorhodomycinone* (**13**). — To a suspension of **6** (6.0 g, 13.50 mmol), **4** (8.51 g, 16.8 mmol), and powdered molecular sieves 4 Å (15 g) in 10:1 dichloromethane–acetone (700 mL) was added Me_3Si triflate (4.97 g, 22.4 mmol) at −35°. After stirring for 6 h, the mixture was worked-up as described for **9**. Column chromatography (200:10:1 chloroform–ethyl acetate–formic acid) of the product on silica gel (550 g) gave **12** (8.25 g, 74.6%) and **13** (0.87 g, 5.4%).

Compound **12** had m.p. 220–224°, $[\alpha]_D$ +46° (*c* 0.007); lit.[2] m.p. 218–223°, $[\alpha]_D$ +46°.

Compound **13** had m.p. 198°, $[\alpha]_D$ +157° (*c* 0.007); lit.[1] m.p. 195–197°, $[\alpha]_D$ +135°.

7-O-*(3-Amino-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyl)-ε-rhodomycinone* (**16**). — To a solution of **9** (7.0 g, 8.72 mmol) in 3:1 chloroform–methanol (80 mL) was added dropwise M NaOH (30 mL). After the addition of methanol to homogenise the mixture, it was stirred for 30 min, neutralised (pH 7.5) with M HCl (~30 mL), and concentrated *in vacuo*. A solution of the residue in 3:1 chloroform–1-butanol (80 mL) was washed with saturated aqueous NaCl (200 mL × 2, pH 8), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (65:35:1 chloroform–methanol–conc. NH_3) of the crude product on silica gel (175 g) gave **16** (3.57 g, 73.6%), m.p. 164–166°, $[\alpha]_D$ +105° (*c* 0.03). ^{1}H-N.m.r. data (300 MHz, MeOD): δ 7.58 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 7.52 (dd, 1 H, $J_{2,3}$ 8.0 Hz, H-2), 7.09 (d, 1 H, H-3), 5.49 (s, 1 H, H-1′), 5.11 (d, 1 H, $J_{7,8B}$ 4.5 Hz, H-7), 4.27 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5′), 4.30 (s, 1 H, H-10), 3.71 (s, 3 H, COOMe), 3.67 (d, 1 H, $J_{3',4'}$ 2.2 Hz, H-4′), 3.51 (ddd, 1 H, $J_{2'ax,3'}$ 12.0, $J_{2'eq,3'}$ 5.0 Hz, H-3′), 2.34 (d, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.19 (dd, 1 H, H-8B), 2.06 (ddd, 1 H, $J_{1',2'ax}$ 3.0, $J_{2'ax,2'eq}$ 12.2 Hz, H-2′ax), 1.97 (dd, 1 H, H-2′eq), 1.83 (m, 1 H, $J_{13A,14}$ 7.5, $J_{13A,13B}$ 15.0 Hz, H-13A), 1.49 (m, 1 H, H-13B), 1.30 (d, 3 H, H-6′,6′,6′), 1.13 (t, 3 H, H-14,14,14). F.a.b.-mass spectrum: *m/z* 558 ($M + H^+$).

Anal. Calc. for $C_{28}H_{31}NO_{11}$ (557.56): C, 60.32; H, 5.60; N, 2.51. Found: C, 60.16; H, 5.65; N, 2.45.

7-O-*(3-Amino-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyl)-ε-isorhodomycinone* (**17**). — Treatment of **12** (5.0 g, 6.10 mmol), as described for **16**, yielded **17** (2.87 g, 82%), m.p. 180°, $[\alpha]_D$ +483° (*c* 0.006); lit.[1] m.p. 178–180°, $[\alpha]_D$ +405° (methanol).

7-O-*[2,3,6-Trideoxy-3-(morpholin-4-yl)-α-*L*-lyxo-hexopyranosyl]-ε-rhodomycinone* (**19**) *and* 7-O-*[3-(3*(R/S)*-cyanomorpholin-4-yl)-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyl]-ε-rhodomycinone* [**21**(R/S)]. — To a solution of **16** (200 mg, 0.36 mmol) and 2,2′-oxydiacetaldehyde[23] (**18**; 75.6 mg, 0.74 mmol) in methanol (30 mL) was added sodium cyanoborohydride (47 mg). After stirring for 24 h, the mixture was worked-up as described by the above general procedure. Column chromatography (5:5:1 chloroform–light petroleum–MeOH) of the residue on silica gel (35 g) afforded **19** (140 mg, 62%) and **21**(*R*/*S*) (30 mg, 13%).

Compound **19** had m.p. 162–165°, $[\alpha]_D$ +384° (*c* 0.0125). ^{1}H-N.m.r. data (200 MHz): δ 13.45, 12.82, and 12.09 (3 s, 3 H, HO-4,6,11), 7.82 (dd, 1 H, $J_{1,2}$ 7.5, $J_{1,3}$ 1.8 Hz, H-1), 7.65 (dd, 1 H, $J_{2,3}$ 8.4 Hz, H-2), 7.26 (dd, 1 H, H-3), 5.46 (bs, 1 H, H-1′), 5.19 (dd, 1 H, $J_{7,8A}$ 2.3, $J_{7,8B}$ 4.3 Hz, H-7), 4.39 (s, 1 H, HO-9), 4.22 (s, 1 H, H-10), 4.02 (q, 1 H, $J_{5',6'}$ 6.5

Hz, H-5'), 3.67 (s, 3 H, COOMe), 3.64 (m, 2 H, H-2''ax,6''ax), 3.63 (s, 1 H, H-4'), 2.94 (bs, 1 H, HO-4'), 2.53 (m, 2 H, H-3''ax,4''ax), 2.51 (m, 1 H, H-3'), 2.51 (m, 2 H, H-2''eq,6''eq), 2.38 (m, 2 H, H-3''eq,5''eq), 2.32 (d, 1 H, H-8A), 2.16 (dd, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8B), 1.84–1.76 (m, 2 H, H-2'ax,2'eq), 1.79 (m, 1 H, $J_{13A,14}$ 7.3, $J_{13A,13B}$ 15.0 Hz, H-13A), 1.38 (m, 1 H, H-13B), 1.33 (d, 3 H, H-6',6',6'), 1.07 (t, 3 H, H-14,14,14).

Anal. Calc. for $C_{32}H_{37}NO_{12}$ (627.65): C, 61.24; H, 5.94; N, 2.23. Found: C, 61.02; H, 5.92; N, 2.09.

Compounds **21**(*R*/*S*) had m.p. 172–174°. F.a.b.-mass spectrum: *m*/*z* 653 (M + H^+), 626 (M − CN).

Anal. Calc. for $C_{33}H_{36}N_2O_{12}$ (652.66): C, 60.73; H, 5.56; N, 4.29. Found: C, 60.65; H, 5.55; N, 4.21.

*7-O-[2,3,6-Trideoxy-3-(morpholin-4-yl)-α-*L*-lyxo-hexopyranosyl]-ε-isorhodomycinone* (**20**) *and 7-O-[3-(3-*(R/S)*-cyanomorpholin-4-yl)-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyl]-ε-isorhodomycinone* [**22**(*R*/*S*]. — To a solution of **17** (200 mg, 0.35 mmol) and **18** (76.0 mg, 0.75 mmol) in methanol (30 mL) was added sodium cyanoborohydride (47 mg). After stirring for 24 h, the mixture was worked-up as described in the above general procedure. Column chromatography of the residue on silica gel afforded **20** (126 mg, 56%) and **22** (*R*/*S*) (35 mg, 15%).

Compound **20** had m.p. 173–175°, $[\alpha]_D$ +530° (*c* 0.01). ^{1}H-N.m.r. data (300 MHz): δ 12.92, 12.75, 12.34, and 12.28 (4 s, 4 H, HO-1,4,6,11), 7.22 (s, 2 H, H-2,3), 5.47 (s, 1 H, H-1'), 5.18 (bs, 1 H, H-7), 4.21 (s, 1 H, H-10), 4.02 (q, 1 H, $J_{5',6'}$ 6.4 Hz, H-5'), 3.66 (m, 2 H, H-2''ax,6''ax), 3.65 (s, 3 H, COOMe), 3.62 (s, 1 H, H-4'), 3.60 (m, 2 H, H-3''ax,4''ax), 2.52 (m, 1 H, H-3'), 2.52 (m, 1 H, H-2''eq,6''eq), 2.38 (m, 2 H, H-3''eq,5''eq), 2.32 (d, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.16 (dd, 1 H, $J_{7,8B}$ 4.0 Hz, H-8B), 1.84–1.76 (m, 2 H, H-2'ax,2'eq), 1.77 (m, 1 H, $J_{13A,14}$ 7.3, $J_{13A,13B}$ 15.0 Hz, H-13A), 1.38 (m, 1 H, H-13B), 1.32 (d, 3 H, H-6',6',6'), 1.07 (t, 3 H, H-14,14,14).

Anal. Calc. for $C_{32}H_{37}NO_{13}$ (643.65): C, 59.72; H, 5.79; N, 2.18. Found: C, 59.62; H, 5.83; N, 2.12.

Compound **22**(*R*/*S*) had m.p. 178–180°, $[\alpha]_D$ +654° (*c* 0.01). F.a.b.-mass spectrum: *m*/*z* 669 (M + H^+), 642 (M − CN).

Anal. Calc. for $C_{33}H_{36}N_2O_{13}$ (668.66): C, 59.28; H, 5.43; Found: C, 59.14; H, 5.41.

7-O-{2,3,6-Trideoxy-3-[6(S)*-hydroxymethyl-2*(S)*-methoxymorpholin-4-yl]-α-*L*-lyxo-hexopyranosyl}-ε-rhodomycinone* (**25**). — The reaction of **16** (1.30 g, 2.33 mmol) with **23** (0.78, 4.81 mmol), as described in the general procedure above, gave **25** (1.24 g, 77.7%), m.p. 130° (dec. 200°), $[\alpha]_D$ +308° (*c* 0.01). ^{1}H-N.m.r. data (400 MHz): δ 13.51, 12.88, and 12.16 (3 s, 3 H, HO-4,6,11), 7.87 (dd, 1 H, $J_{1,2}$ 7.6, $J_{1,3}$ 1.2 Hz, H-1), 7.71 (dd, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 7.32 (dd, 1 H, H-3), 5.52 (bs, 1 H, H-1'), 5.24 (dd, 1 H, $J_{7,8A}$ 1.5, $J_{7,8B}$ 4.0 Hz, H-7), 4.67 (bs, 1 H, H-2''), 4.42 (s, 1 H, H-10), 4.28 (s, 1 H, HO-9), 4.07 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5'), 3.97 (m, 1 H, H-5''), 3.72 (s, 3 H, COOMe), 3.68 (bs, 1 H, H-4'), 3.62 (dd, 1 H, $J_{6'',CH\text{-}6''A}$ 3.6, $J_{CH\text{-}6''A,CH\text{-}6''B}$ 11.6 Hz, CH-6''A), 3.53 (dd, 1 H, $J_{6'',CH\text{-}6''B}$ 5.4 Hz, CH-6''B), 3.35 (s, 3 H, MeO-2''), 3.06 (d, 1 H, $J_{3''ax,3''eq}$ 11.6 Hz, H-3''eq), 2.76 (d, 1 H, $J_{5''ax,5''eq}$ 10.9 Hz, H-5''eq), 2.37 (ddd, 1 H, $J_{7,8A}$ 1.5, $J_{8A,10}$ 1.5, $J_{8''A,8''B}$ 14.9 Hz, H-8A), 2.37 (m, 1 H, H-3'), 2.23 (dd, 1 H, $J_{7,8B}$ 4.0 Hz, H-8B), 2.15 (dd, 1 H, $J_{2'',3''ax}$ 2.5 Hz, H-3''ax),

2.08 (dd, 1 H, $J_{5''ax,6''}$ 10.9 Hz, H-5''ax), 1.83 (m, 1 H, $J_{13A,14}$ 7.3, $J_{13''A,13''B}$ 14.8 Hz, H-13A), 1.84–1.80 (m, 2 H, H-2'ax,2'eq), 1.46 (m, 1 H, H-13B), 1.38 (d, 3 H, H-6',6',6'), 1.13 (t, 3 H, H-14,14,14).

Anal. Calc for $C_{34}H_{41}NO_{14}$ (687.70): C, 59.38; H, 2.04; N, 2.04. Found: C, 59.25; H, 2.07; N, 1.93.

7-O-{2,3,6-Trideoxy-3-[6(S)-hydroxymethyl-2(S)-methoxymorpholin-4-yl]-α-L-lyxo-hexopyranosyl}-ε-isorhodomycinone (**26**). — The reaction of **17** (2.20 g, 3.83 mmol) with **23** (1.26 g, 7.80 mmol), as described in the general procedure above, gave **26** (2.17 g, 80.3%), m.p. 198–200°, $[\alpha]_D$ +400° (*c* 0.05). ^{1}H-N.m.r. data (300 MHz): δ 12.96, 12.81, 12.29, and 12.29 (4 s, 4 H, HO-1,4,6,11), 7.28 (s, 2 H, H-2,3), 5.51 (bs, 1 H, H-1'), 5.23 (dd, 1 H, $J_{7,8A}$ 1.5, $J_{7,8B}$ 3.5 Hz, H-7), 4.67 (s, 1 H, H-2''), 4.46 (s, 1 H, H-10), 4.27 (s, 1 H, HO-9), 4.07 (q, 1 H, $J_{5',6'}$ 6.5 Hz, H-5'), 3.99 (m, 1 H, H-6''), 3.72 (s, 3 H, COOMe), 3.68 (bs, 1 H, H-4'), 3.63 (dd, 1 H, $J_{6'',CH\text{-}6''A}$ 4.0, $J_{CH\text{-}6''A,CH\text{-}6''B}$ 11.5 Hz, CH-6''A), 3.52 (dd, 1 H, $J_{6'',CH\text{-}6''B}$ 5.0 Hz, CH-6''B), 3.35 (s, 3 H, MeO-2''), 3.06 (d, 1 H, $J_{3''ax,3''eq}$ 12.0 Hz, H-3''eq), 2.78 (d, 1 H, $J_{5''ax,5''eq}$ 11.0 Hz, H-5''eq), 2.38 (bd, 1 H, $J_{8A,8B}$ 15.0 Hz, H-8A), 2.37 (m, 1 H, H-3'), 2.23 (dd, 1 H, H-8B), 2.15 (dd, 1 H, $J_{2'',3''ax}$ 2.0 Hz, H-3''ax), 2.08 (dd, 1 H, $J_{5''ax,6''}$ 11.0 Hz, H-5''ax), 1.85 (m, 1 H, $J_{13A,14}$ 7.2, $J_{13A,13B}$ 15.0 Hz, H-13A), 1.84 (bs, 2 H, H-2'ax,2'eq), 1.46 (m, 1 H, H-13B), 1.38 (d, 3 H, H-6',6',6'), 1.13 (t, 1 H, H-14,14,14). F.a.b.-mass spectrum: *m/z* 704 ($M + H^+$).

Anal. Calc. for $C_{34}H_{41}NO_{15}$ (703.70): C, 58.03; H, 5.87; N, 1.99. Found: C, 58.12; H, 5.88; N, 1.91.

7-O-{2,3,6-Trideoxy-3-[6(S)-hydroxymethyl-2(R)methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl}-ε-rhodomycinone (**27**). — The reaction of **16** (300 mg, 0.53 mmol) with **24** (194 mg, 1.20 mmol), as described in the general procedure above, gave **27** (0.30 g, 82.1%), m.p. 155–158°, $[\alpha]_D$ +410° (*c* 0.01). ^{1}H-N.m.r. data (400 MHz): δ 13.42, 12.82, and 12.09 (3 s, 3 H, HO-4,6,11), 7.80 (dd, 1 H, $J_{1,2}$ 7.6, $J_{1,3}$ 1.3 Hz, H-1), 7.64 (dd, 1 H, $J_{2,3}$ 8.2 Hz, H-2), 7.24 (dd, 1 H, H-3), 5.45 (bs, 1 H, H-1), 5.17 (dd, 1 H, $J_{7,8A}$ 1.8, $J_{7,8B}$ 4.1 Hz, H-7), 4.41 (dd, 1 H, $J_{2'',3''ax}$ 7.9, $J_{2'',3''eq}$ 2.2 Hz, H-2''), 4.30 (s, 1 H, H-10), 4.01 (q, 1 H, $J_{5',6'}$ 6.6 Hz, H-5'), 3.65 (s, 3 H, COOMe), 3.65 (s, 1 H, H-4'), 3.63 (d, 1 H, CH-6''A), 3.53 (d, 1 H, $J_{6'',CH\text{-}6''A}$ 6.0, $J_{CH\text{-}6''A,CH\text{-}6''B}$ 12.5 Hz, CH-6''B), 3.45 (m, 1 H, H-6''), 3.42 (s, 3 H, MeO-2''), 2.97 (d, 1 H, $J_{3''ax,3''eq}$ 10.6 Hz, H-3''eq), 2.62 (d, 1 H, $J_{5''ax,5''eq}$ 11.1 Hz, H-5''eq), 2.36 (m, 1 H, H-3'), 2.30 (d, 1 H, $J_{8A,8B}$ 15.2 Hz, H-8A), 2.17 (dd, 1 H, H-8B), 2.03 (dd, 1 H, $J_{5''ax,6''}$ 8.8 Hz, H-5''ax), 1.86 (dd, 1 H, H-3''ax), 1.78 (m, 1 H, $J_{13A,14}$ 7.5, $J_{13A,13B}$ 15 Hz, H-13A), 1.75 (m, 1 H, H-2'ax,2'eq), 1.39 (m, 2 H, H-13B), 1.31 (d, 3 H, H-6',6',6'), 1.06 (t, 3 H, H-14,14,14).

Anal. Calc. for $C_{34}H_{41}NO_{14}$ (687.70): C, 59.38; H, 2.04; N, 2.04. Found: C, 59.28; H, 2.05; N, 1.99.

7-O-{2,3,6-Trideoxy-3-[6(S)-hydroxymethyl-2(R)-methoxy-4-morpholinyl]-α-L-lyxo-hexopyranosyl}-ε-isorhodomycinone (**28**). — The reaction of **17** (300 mg, 0.52 mmol) with **24** (194 mg, 120 mmol), as described in the general procedure above, gave **28** (291 mg, 79.6%), m.p. 108–110°, $[\alpha]_D$ +555° (*c* 0.06). ^{1}H-N.m.r. data (400 MHz): δ 12.92, 12.77, 12.24, and 12.09 (4 s, 4 H, HO-1,4,6,11), 7.23 (s, 2 H, H-2,3), 5.45 (bs, 1 H, H-1), 5.17 (dd, 1 H, $J_{7,8A}$ 1.8, $J_{7,8B}$ 4.1 Hz, H-7), 4.41 (dd, 1 H, $J_{2'',3''ax}$ 7.9, $J_{2'',3''eq}$ 2.2 Hz,

H-2″), 4.30 (s, 1 H, H-10), 4.01 (q, 1 H, $J_{5',6'}$ 6.6 Hz, H-5′), 3.65 (s, 3 H, COOMe), 3.65 (s, 1 H, H-4′), 3.63 (d, 1 H, CH-6′A), 3.53 (d, 1 H, $J_{6'',CH\text{-}6''A}$ 6.0, $J_{CH\text{-}6''A,CH\text{-}6''B}$ 12.5 Hz, CH-6″B), 3.45 (m, 1 H, H-6″), 3.42 (s, 3 H, MeO-2″), 2.97 (d, 1 H, $J_{3''ax,3''eq}$ 10.6 Hz, H-3″eq), 2.62 (d, 1 H, $J_{5''ax,5''eq}$ 11.1 Hz, H-5″eq), 2.36 (m, 1 H, H-3′), 2.30 (d, 1 H, $J_{8A,8B}$ 15.2 Hz, H-8A), 2.17 (dd, 1 H, H-8B), 2.03 (dd, 1 H, $J_{5''ax,6''}$ 8.8 Hz, H-5″ax), 1.86 (dd, 1 H, H-3″ax), 1.78 (m, 1 H, $J_{13A,14}$ 7.5, $J_{13A,13B}$ 15 Hz, H-13A), 1.75 (m, 1 H, H-2′ax,2′eq), 1.39 (m, 2 H, H-13B), 1.31 (d, 3 H, H-6′,6′,6′), 1.06 (t, 3 H, H-14,14,14). F.a.b.-mass spectrum: *m/z* 704 ($M + H^+$).

Anal. Calc for $C_{34}H_{41}NO_{15}$ (703.70): C, 58.03; H, 5.87; N, 1.99. Found: C, 58.17; H, 5.89; N, 1.90.

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