SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME ESTERS OF THE *N*-ACETYLGLUCOSAMINYL AGLYCONE AND OF THE AGLYCONE OF TEICOPLANIN

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A series of ester derivatives of teicoplanin-*N*-acetylglucosaminyl aglycone (T-A3-2) and deglucoteicoplanin was prepared starting from teicoplanin and from the corresponding deglycosylation compounds.

The modification of the ionic and lipophilic character of the parent antibiotic strongly influences the spectrum of antibacterial activity *in vitro*.

Some clinical problems due to the appearance of methicillin-resistant Staphylococci in recent years have stimulated the search for new glycopeptide antibiotics belonging to the vancomycin-ristocetin family. As a result of this effort, a large number of structurally related molecules have been obtained by fermentation of microorganisms isolated from soil samples. Among them, teicoplanin (**I**), a complex of five factors (T-A2-1 to 5) (Fig. 1), is characterized by the presence of glycolipid units, formed by one glucosamine *N*-acylated with aliphatic chains.[1]

Teicoplanin is a very effective drug for the treatment of serious illnesses caused by Gram-positive bacteria.[2,3] It has been extensively studied clinically and will soon be available for therapeutic use.

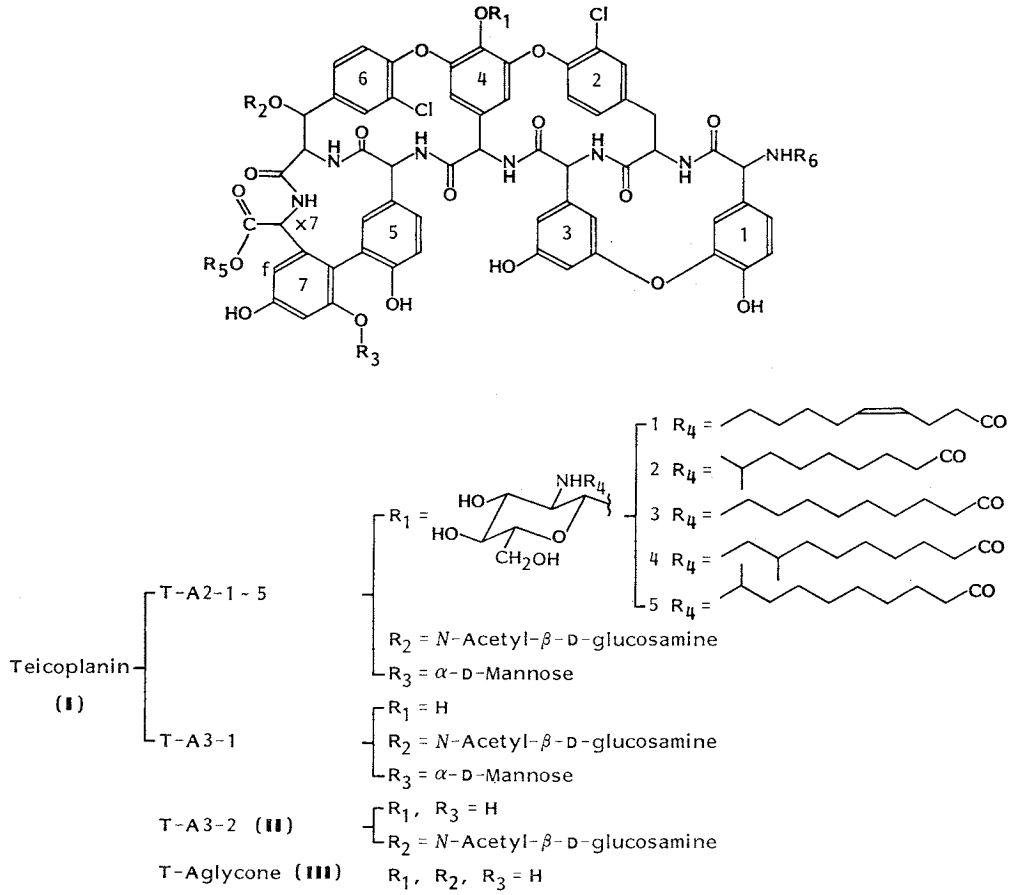
The knowledge of the structures of many glycopeptides,[4] of the common molecular basis of action,[1,4~6] and of the correlation between pharmacokinetics and physico-chemical properties[7~13] have offered ground for oriented semisynthetic modifications. In this paper a series of esters of the *N*-acetylglucosaminyl aglycone (T-A3-2, **II**)[14] and of the aglycone (**III**)[14,15] (Fig. 1) of teicoplanin is described.

Chemistry

In previous papers,[14,15] it has been described that teicoplanin (**I**) gives upon hydrolysis the pseudoaglycones T-A3-1 and T-A3-2 (**II**) and the aglycone (**III**) (Fig. 1). The conditions of this reaction are critical since either epimerization at an amino acid center[16] or the opening of the polypeptide chain[17] may occur. Also the esterification reaction has to be carefully controlled to avoid the side reactions mentioned. Although the general procedures are common, the solvents and the overall conditions of the esterification vary from compound to compound as well as the purification procedures.

The methods for the preparation of the esters of T-A3-2 (**II**) reported in Table 1 are outlined in Scheme 1. The reactions were carefully monitored by HPLC. Treatment of teicoplanin (**I**) with HCl in THF gave the 4-chlorobutyl ester (**Vf**) by removing the *N*-acylglucosamines and mannose and by concomitant esterification of the carboxyl with the tetramethylene chlorohydrin generated from THF (Method A). Reaction of **II** with methyl, ethyl and butyl alcohol in the presence of anhydrous HCl led to the corresponding esters **Va**, **Vb** and **Ve** (Method B). The 2-chloroethyl ester (**Vc**) was obtained from a solution of **II** in 2-chloroethanol in the presence of thionyl chloride (Method C).

Fig. 1. Structures of the components of teicoplanin, the pseudo-aglycones and the aglycone (R_5, R_6=H).



A different approach was required for the preparation of 2-hydroxyethyl, benzyl and 4-methylbenzyl esters (**Vd**, **Vg** and **Vh**). The corresponding halogeno alkyls or aryls were allowed to react in DMF in the presence of $KHCO_3$ with the intermediate **IV** obtained from **II** by protecting the free amino group as *N-tert*-butyloxycarbonyl (*N*-BOC). TFA was used to remove the protecting group without cleavage of the glycosidic linkage with *N*-acetylglucosamine (Method D).

The esters of deglucoteicoplanin (**III**) are listed in Table 2. Method A described previously was also suitable for the preparation of 4-chlorobutyl ester of deglucoteicoplanin (**VIIIh**) from teicoplanin (**I**), the only difference being the reaction time (Scheme 2). Method B was applied to **II** for the preparation of compounds **VIIIg**, **VIIIi**, **VIIIl** and **VIIIn**; here again the removal of the *N*-acetylglucosamine is concomitant with the esterification of the carboxyl group.

Deglucoteicoplanin (**III**) was the starting material for the preparation of the other esters. Refluxing **III** in 2-methoxyethanol in the presence of H_2SO_4 and molecular sieves gave **VIIIf** (Method E).

Two different protecting groups, namely *N*-benzoxycarbonyl (*N*-CBZ) and *N*-BOC, were used for the synthesis of the two versatile intermediates **VI** and **VII**. From **VI**, *N*-CBZ-deglucoteicoplanin esters **VIb**~**VId** and **VIm** were obtained which were converted by catalytic hydrogenolysis into the corresponding esters **VIIIb**~**VIIId** and **VIIIm** (Method F). The synthesis of the esters **VIIIa**, **VIIIe**

Table 1. Derivatives of T-A3-2 (II, Fig. 1).

Compound	R_5	R_6	Yield (%)	Method[a]	HPLC[b,c] t_R (minutes)	pK_{MCS}[b]	IR (cm^{-1})[b] $\nu_{C=O}$, ester	Formula[b]	MW
IV	H	BOC	87.3	—	38.4	nd	nd	$C_{71}H_{66}Cl_2N_8O_{25}$	1,502.3
Va	CH_3	H	64.3	B	20.3	6.70	1720	$C_{67}H_{60}Cl_2N_8O_{23}\cdot HCl$	1,452.6
Vb	C_2H_5	H	39.2	B	22.0	6.68	1720	$C_{68}H_{62}Cl_2N_8O_{23}\cdot HCl$	1,466.7
Vc	$Cl(CH_2)_2$	H	18.6	C	23.1	6.67	1725	$C_{68}H_{61}Cl_3N_8O_{23}\cdot HCl$	1,501.2
Vd	$HO(CH_2)_2$	H	78.0	D	18.9	nd	1740	$C_{68}H_{62}Cl_2N_8O_{24}\cdot CF_3COOH$	1,560.2
Ve	n-C_4H_9	H	34.1	B	23.3	6.65	1715	$C_{70}H_{66}Cl_2N_8O_{23}\cdot HCl$	1,494.7
Vf	$Cl(CH_2)_4$	H	30.7	A	30.5	6.66	1720	$C_{70}H_{65}Cl_3N_8O_{23}\cdot HCl$	1,529.2
Vg	$C_6H_5CH_2$	H	88.8	D	29.7	nd	1735	$C_{73}H_{64}Cl_2N_8O_{23}\cdot CF_3COOH$	1,606.3
Vh	p-$CH_3C_6H_4CH_2$	H	33.3	D	33.5	nd	1735	$C_{74}H_{66}Cl_2N_8O_{23}$	1,506.3

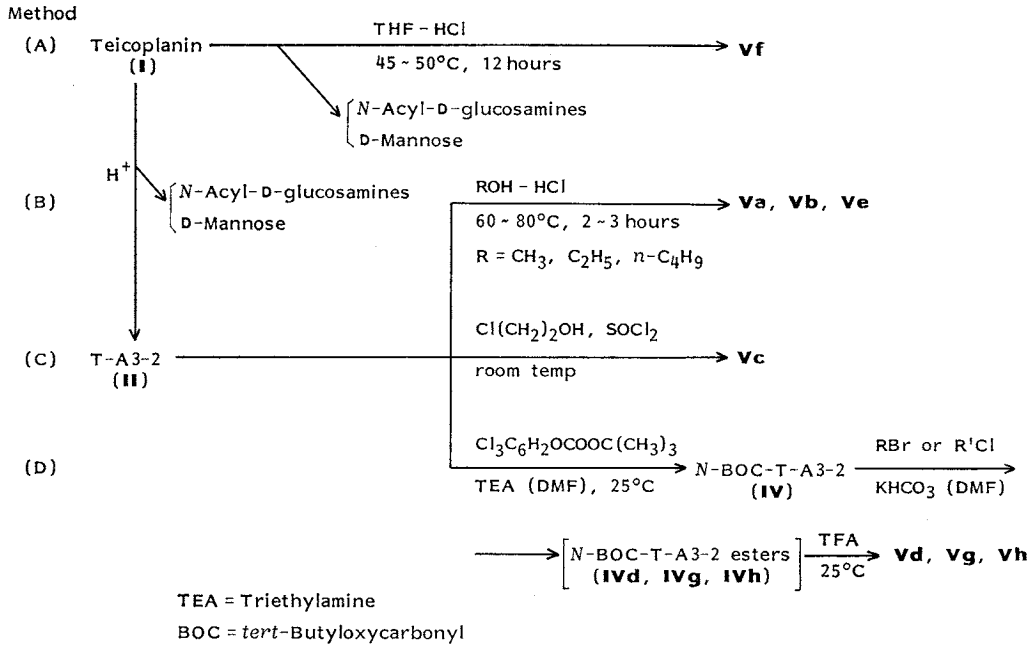
[a] See Scheme 1.

[b] See Experimental section.

[c] Factor A2 of teicoplanin: Retention time (t_R) 26.5 minutes; T-A3-2 (II) 14.4 minutes.

nd: Not determined.

Scheme 1.



and **VIIIo** was accomplished by removing with TFA the protecting group from the corresponding *N*-BOC-deglucoteicoplanin esters which were not isolated in a pure state (Method G).

All the esters and intermediates show a UV absorption maximum at 280 nm in MeOH and in acidic medium as teicoplanin (**I**) and starting compounds **II** and **III** do.

The IR spectra are in accordance with the assigned structures and the ν_{CO} ester band is reported in Tables 1 and 2.

^{1}H NMR spectral data of the *N*-protected intermediates **IV**, **VI** and **VII** and of the two series of esters were compared with those assigned in the detailed analysis of the spectrum of deglucoteicoplanin·HCl (**III**).[9] The spectra are in full accordance with the structures assigned. Two main differences appear, *i.e.*, the signals attributed to protons x7 and 7f fall in the intervals 4.50~4.57 ppm and 6.10~6.14 ppm, respectively. Upon comparison with the corresponding signals in the spectra of deglucoteicoplanin (4.42 and 6.24 ppm, respectively) and of T-A3-2 (4.42 and 6.22 ppm, respectively) it can be inferred that the ester group causes an inductive effect (downfield shift) on x7 and an anisotropic effect (upfield shift) on 7f.

Acid-base titration of teicoplanin (**I**) in methyl cellosolve (MCS) - H_2O (4 : 1) shows two ionizable functions, with the apparent constant values *pK* 5.0 and 7.1, and four functions in the range from 9 to 12.5. A complete study demonstrated that they are attributable to the terminal carboxyl and amino groups, respectively, which give rise to a zwitterion, and to four phenolic groups, respectively. The same values are shown for the pseudo-aglycone T-A3-2 (**II**), and similar values for deglucoteicoplanin (**I**) (4.8 and 6.9). The majority of the esters possess only the *pKa* value of the amino group ranging from 6.5 to 6.8, while the basic morpholinyl ester **VIIIo** shows two values 5.3 and 7.5.

Results and Discussion

The rationale for the esterification of the terminal carboxyl group was to increase the lipophilicity

Table 2. Derivatives of deglucoteicoplanin (III, Fig. 1).

Compound	R_5	R_6	Yield (%)	Method[a]	HPLC[b,c] t_R (minutes)	pK_{MCS}[b]	IR (cm^{-1})[b] $\nu_{C=O}$, ester	Formula[b]	MW
VI	H	CBZ	83.1	—	43.1	5.02	1730	$C_{66}H_{51}Cl_2N_7O_{20}$	1,331.1
VIb	C_2H_5	CBZ	82.1	F	47.8	nd	nd	$C_{68}H_{55}Cl_2N_7O_{20}$	1,361.2
VIc	$F(CH_2)_2$	CBZ	31.1	F	nd	nd	1730	$C_{68}H_{54}Cl_2FN_7O_{20}$	1,379.2
VId	$Br(CH_2)_2$	CBZ	73.9	F	48.4	nd	1730	$C_{68}H_{54}BrCl_2N_7O_{20}$	1,440.1[d]
VIm	$(CH_3)_3CCOOCH_2$	CBZ	82.2	F	50.3	nd	1740	$C_{72}H_{61}Cl_2N_7O_{22}$	1,447.2
VII	H	BOC	87.3	—	40.5	5.25	1730	$C_{63}H_{53}Cl_2N_7O_{20}$	1,299.1
VIIIa	CH_3	H	40.4	G	28.0	nd	nd	$C_{59}H_{47}Cl_2N_7O_{18}\cdot CF_3COOH$	1,327.0
VIIIb	C_2H_5	H	92.9	F	30.9	nd	1730	$C_{60}H_{49}Cl_2N_7O_{18}$	1,227.0
VIIIc	$F(CH_2)_2$	H	13.5	F	48.4	nd	1735	$C_{60}H_{48}Cl_2FN_7O_{18}\cdot HCl$	1,281.5
VIIId	$Br(CH_2)_2$	H	8.3	F	34.4	nd	1740	$C_{60}H_{48}BrCl_2N_7O_{18}\cdot HCl$	1,342.4
VIIIe	$HO(CH_2)_2$	H	36.1	G	25.7	nd	nd	$C_{60}H_{49}Cl_2N_7O_{19}\cdot CF_3COOH$	1,357.1
VIIIf	$CH_3O(CH_2)_2$	H	14.7	E	29.6	nd	1730	$C_{61}H_{51}Cl_2N_7O_{19}$	1,257.1
VIIIg	n-C_4H_9	H	60.2	B	30.0	6.57	1720	$C_{62}H_{53}Cl_2N_7O_{18}\cdot HCl$	1,291.6
VIIIh	$Cl(CH_2)_4$	H	51.1	A	41.1	6.60	1730	$C_{62}H_{52}Cl_3N_7O_{18}$	1,289.5
VIIIi	$CH_3CH(OH)(CH_2)_2$	H	25.3	B	27.9	nd	1725	$C_{62}H_{53}Cl_2N_7O_{19}$	1,271.1
VIIIl	n-C_8H_{17}	H	15.8	B	39.9	6.82	1715	$C_{66}H_{61}Cl_2N_7O_{18}\cdot HCl$	1,347.6
VIIIm	$(CH_3)_3CCOOCH_2$	H	35.1	F	44.8	6.52	1740	$C_{64}H_{55}Cl_2N_7O_{20}\cdot HCl$	1,349.6
VIIIn	$C_6H_5CH_2$	H	23.3	B	31.1	6.67	1730	$C_{65}H_{51}Cl_2N_7O_{18}\cdot HCl$	1,325.6
VIIIo	$O(CH_2)_4N(CH_2)_2$	H	30.8	G	25.9	nd	nd	$C_{64}H_{56}Cl_2N_8O_{19}\cdot 2CF_3COOH$	1,540.2

[a] See Scheme 2.

[b] See Experimental section.

[c] Factor A2 of teicoplanin: Retention time (t_R) 26.5 minutes; deglucoteicoplanin (III) t_R 18.4 minutes.

[d] Confirmed by fast atom bombardment mass spectrum (FAB-MS).

nd: Not determined.

Scheme 2.

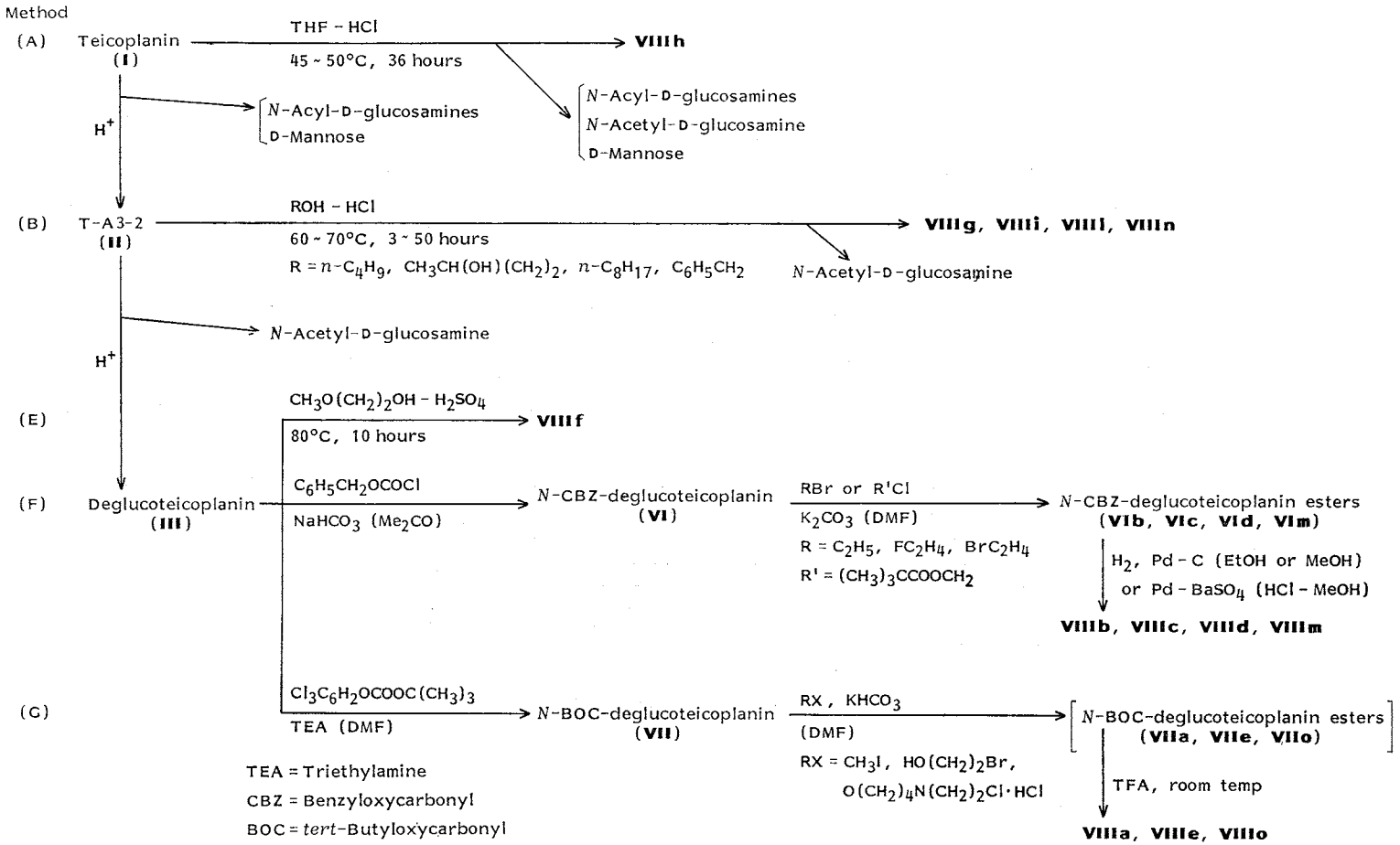

Method
(A) Teicoplanin (I)
THF - HCl
45 ~ 50°C, 36 hours
VIIIh
H+
N-Acyl-D-glucosamines
D-Mannose
N-Acyl-D-glucosamines
N-Acetyl-D-glucosamine
D-Mannose
(B) T-A3-2 (II)
ROH - HCl
60 ~ 70°C, 3 ~ 50 hours
R = n-C4H9, CH3CH(OH)(CH2)2, n-C8H17, C6H5CH2
VIIIg, VIIIi, VIIIl, VIIIn
N-Acetyl-D-glucosamine
H+
N-Acetyl-D-glucosamine
(E)
CH3O(CH2)2OH - H2SO4
80°C, 10 hours
VIIIf
(F) Deglucoteicoplanin (III)
C6H5CH2OCOCl
NaHCO3 (Me2CO)
N-CBZ-deglucoteicoplanin (VI)
RBr or R'Cl
K2CO3 (DMF)
R = C2H5, FC2H4, BrC2H4
R' = (CH3)3CCOOCH2
N-CBZ-deglucoteicoplanin esters (VIb, VIc, VId, VIm)
H2, Pd - C (EtOH or MeOH)
or Pd - BaSO4 (HCl - MeOH)
VIIIb, VIIIc, VIIId, VIIIm
(G)
Cl3C6H2OCOOC(CH3)3
TEA (DMF)
N-BOC-deglucoteicoplanin (VII)
RX, KHCO3
(DMF)
RX = CH3I, HO(CH2)2Br,
O(CH2)4N(CH2)2Cl·HCl
N-BOC-deglucoteicoplanin esters (VIIa, VIIe, VIIo)
TFA, room temp
VIIIa, VIIIe, VIIIo
TEA = Triethylamine
CBZ = Benzyloxycarbonyl
BOC = tert-Butyloxycarbonyl

Table 3. *In vitro* antibacterial activity.[a]

Organism	MIC (μg/ml)										
	Teicoplanin (I)	T-A3-2 (II)	IV	Va	Vb	Vc	Vd	Ve	Vf	Vg	Vh
Staphylococcus aureus TOUR	0.125	0.5	1	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
S. aureus TOUR[b]	0.5	0.5	2	0.25	0.25	0.25	0.125	0.25	0.125	0.125	0.25
S. epidermidis ATCC 12228	0.25	0.125	0.125	0.032	0.032	0.063	0.063	0.032	0.063	0.063	0.063
S. haemolyticus L 602[c]	4	0.5	2	0.25	nd	0.25	0.5	nd	nd	0.25	0.25
Streptococcus pyogenes C203 SKF 13400	0.063	0.5	2	0.125	0.125	0.25	0.25	0.25	0.25	0.125	0.125
S. pneumoniae UC41	0.063	1	1	0.25	0.25	0.25	1	0.25	0.125	0.25	0.5
S. faecalis ATCC 7080	0.125	1	4	0.25	0.25	0.5	0.25	0.25	0.25	0.125	0.25
S. mitis L 796[c]	0.125	1	2	0.25	nd	0.5	0.5	nd	nd	0.125	0.125
Escherichia coli SKF 12140	>128	>128	>128	128	128	128	128	128	128	64	64
Proteus vulgaris X 19 H ATCC 881	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Pseudomonas aeruginosa ATCC 10145	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128

[a] Minimum inhibitory concentration (MIC) was determined using the 2-fold dilution method in microtiter system. The media used were: Iso-Sensitest broth (Oxoid) for Staphylococci, *S. faecalis* and Gram-negative bacteria; Tood-Hewitt broth (Difco) for Streptococci. The final inoculum was about 10^4 cfu/ml. MIC was read as the lowest concentration which showed no visible growth after 18~24 hours incubation at 37°C.

[b] Inoculum 10^6 cfu/ml.

[c] Clinical isolates.

nd: Not determined.

Table 4. *In vitro* antibacterial activity.[a]

Organism	MIC (μg/ml)									
	Teicoplanin (I)	Deglucoteicoplanin (III)	VI	VIb	VIc	VId	VIm	VII	VIIIa	VIIIb
Staphylococcus aureus TOUR	0.125	0.063	0.25	1	0.25	1	1	0.125	0.063	0.125
S. aureus TOUR[b]	0.5	0.125	1	1	0.25	2	2	0.25	0.125	0.25
S. epidermidis ATCC 12228	0.25	0.016	0.063	0.063	0.063	0.125	0.25	0.063	0.032	0.032
Streptococcus pyogenes C203 SKF 13400	0.063	0.125	0.125	0.125	0.125	0.25	0.5	0.25	0.125	0.125
S. pneumoniae UC41	0.063	0.125	0.125	0.125	0.125	0.5	1	0.25	0.125	0.125
S. faecalis ATCC 7080	0.125	0.125	2	1	1	2	2	0.5	0.125	0.25
Escherichia coli SKF 12140	>128	64	>128	>128	>128	>128	>128	>128	16	32
Proteus vulgaris X 19 H ATCC 881	>128	128	>128	>128	>128	>128	>128	>128	>128	>128
Pseudomonas aeruginosa ATCC 10145	>128	>128	>128	>128	>128	>128	>128	>128	128	>128

Organism	MIC (μg/ml)										
	VIIIc	VIIId	VIIIe	VIIIf	VIIIg	VIIIh	VIIIi	VIIIl	VIIIm	VIIIn	VIIIo
Staphylococcus aureus TOUR	0.063	0.063	0.063	0.125	0.125	0.125	0.125	0.25	0.125	0.5	0.125
S. aureus TOUR[b]	0.125	0.125	0.125	0.25	0.5	0.125	0.25	0.5	0.5	0.5	0.25
S. epidermidis ATCC 12228	0.016	0.063	0.016	0.063	0.063	0.063	0.063	0.125	0.063	0.125	0.063
Streptococcus pyogenes C203 SKF 13400	0.063	0.063	0.125	0.125	0.125	0.125	0.125	0.063	0.125	0.063	0.125
S. pneumoniae UC41	0.125	0.125	0.125	0.25	0.063	0.125	0.125	0.063	0.125	0.25	0.125
S. faecalis ATCC 7080	0.125	0.125	0.125	0.125	0.25	0.25	0.125	0.5	0.5	0.5	0.125
Escherichia coli SKF 12140	16	16	16	32	64	32	32	>128	>128	8	>128
Proteus vulgaris X 19 H ATCC 881	>128	32	>128	>128	nd	>128	128	>128	>128	>128	>128
Pseudomonas aeruginosa ATCC 10145	64	64	64	128	nd	>128	128	>128	>128	>128	>128

[a] See footnote to Table 3.
[b] Inoculum 10^6 cfu/ml.
nd: Not determined.

and to modify the ionization behavior of T-A3-2 (**II**) and deglucoteicoplanin (**III**), which were chosen because they are single products obtained fairly easily from the teicoplanin complex.

The *in vitro* antibacterial activity (MIC) of the parent antibiotics and of the derivatives synthesized are reported in Tables 3 and 4. The pseudo-aglycone T-A3-2 (**II**) shows activity comparable to that of teicoplanin against Staphylococci and a better activity against *Staphylococcus haemolyticus*; against Streptococci it is less active (Table 3). T-A3-2 is less active than teicoplanin by subcutaneous administration in the mouse model of *Streptococcus pyogenes* septicemia.[14] The *pKa* of T-A3-2 does not differ from that of teicoplanin, while it appears somewhat less lipophilic than teicoplanin based on the reverse-phase HPLC retention times. Thus, this seems to be the main factor affecting the biological action of T-A3-2.

Among the derivatives, the blocking of the NH_2 (compound **IV**) leads to a very slight decrease of the MIC against a few strains, confirming the observation that the influence of the *N*-terminus seems to consist only in favoring the initial complex action with the D-alanyl-D-alanine terminal of the receptor.[18,19] All the esters of T-A3-2 are generally more active than the parent teicoplanin and T-A3-2 against *Staphylococcus epidermidis*; against *S. haemolyticus* they show activity comparable with that of T-A3-2. All the derivatives inhibited *Escherichia coli* at concentrations of 64~128 μg/ml.

Deglucoteicoplanin (**III**) is as active *in vitro* as teicoplanin against Gram-positive bacteria; in particular, it shows a higher activity against *S. epidermidis* (Table 4). Here again an activity appears against *E. coli* and *Proteus vulgaris*. In *S. pyogenes* septicemia, it shows a good efficacy.[14] The total charge is not substantially modified with respect to teicoplanin, whereas the hydrophobic character lies between that of T-A3-2 and that of teicoplanin.

The blocking of the terminal NH_2 with or without esterification of the carboxyl group (compounds **VI**, **VIb**~**VId**, **VIm** and **VII**) gives only a small effect on the *in vitro* antibacterial activity, except against *Streptococcus faecalis* and, for compounds **VIb**, **VId** and **VIm**, against *Staphylococcus aureus*. The *in vitro* activities of the esters are comparable to that of deglucoteicoplanin against Staphylococci and Streptococci; compounds **VIIIa** to **VIIIi** and, in particular, the benzyl ester **VIIIn** show definitely better activity against *E. coli*. Compounds **VIIIa**, **VIIIc**~**VIIIf** and **VIIIi** exhibit also activity against the other Gram-negative bacteria.

In conclusion, the modifications of the terminal carboxyl of pseudo-aglycone T-A3-2 (**II**) and of deglucoteicoplanin (**III**) provided some derivatives exhibiting in general a better activity against coagulase-negative Staphylococci and a certain degree of activity against Gram-negative bacteria, particularly against *E. coli*.

More detailed studies will give further information for the oriented synthesis of new teicoplanin derivatives.

Experimental

Evaporation of solvents was carried out, after addition of BuOH to prevent foaming, with a rotary evaporator at 45°C under vacuum. If not otherwise stated the intermediates and the final products were washed with Et_2O and dried at 40°C under vacuum.

Column chromatography was performed using Silica gel 60 (0.06~0.2 mm), silanized Silica gel 60 (0.06~0.2 mm) or Silica gel RP-8 (LiChroprep 40~63 μm) (Merck).

HPLC was applied to monitor reactions, chromatographic fractions, and purity of the compounds using a Hewlett-Packard 1084A chromatograph equipped with a UV detector at 254 nm and Hibar LiChrosorb RP-8 (150 mm, 5 μm) column and the following variables: Injection volume, 20 μl;

flow rate, 1 ml/minute; mobile phases, (A) CH_3CN - 0.02 M aq NaH_2PO_4 (5 : 95), (B) CH_3CN - 0.02 M aq NaH_2PO_4 (75 : 25); linear step-gradient as follows:

Minutes	0	40	45	48	55	56.
% B	8	40	60	60	8	—.

All compounds were analyzed for C, H and N on samples previously dried at 140°C under N_2 atmosphere. Weight loss was determined by thermogravimetric analysis (TGA) at 140°C; inorganic residue was determined after heating the samples at 900°C in O_2 atmosphere. Cl, Br and F, when present, were determined on samples dried as described above. The analytical results were in accordance with the theoretical values.

The pK_{MCS} values were determined potentiometrically in MCS - H_2O (4 : 1) solution. An excess of 0.01 N HCl in the same solvent mixture was added and the resulting solution was titrated with 0.01 N NaOH in the same solvent mixture.

The IR spectra were obtained in a Nujol mull with a Perkin-Elmer 850 instrument.

The ^1H NMR spectra were obtained with a Bruker instrument AM 250 equipped with an Aspect 3000 console at 250 MHz. The spectra were recorded at 40°C in DMSO-d_6 solution (internal standard TMS, δ 0.00 ppm).

Esters of T-A3-2 (**II**)

4-Chlorobutyl Ester, Hydrochloride (**Vf**)

Dry HCl was bubbled for 12 hours into a stirred suspension of teicoplanin* (**I**, 10 g) in 200 ml of THF while maintaining the temp at 45~50°C. The clear solution was poured into 900 ml of Et_2O and the solid, which separated, was collected by filtration, washed with Et_2O and dried over KOH pellets yielding 6 g of the crude ester, which was dissolved in 1.5 ml of a mixture of BuOH - MeOH - H_2O (3 : 2 : 1). Silanized silica gel was added and the solvents were removed under vacuum at 45°C. The residue was suspended in 400 ml of a mixture of H_2O - CH_3CN (9 : 1) and applied at the top of a chromatographic column prepared with 1.4 kg of the same silica gel, pre-equilibrated with 1 liter of 1% aq $HCOONH_4$ at pH 4.2 and stabilized with 200 ml of a mixture H_2O - CH_3CN (9 : 1). The column was washed with 1 liter of the same mixture, then developed with a stepwise gradient from 10% to 50% of CH_3CN in H_2O at a rate of 400 ml/hour. Fractions of about 20 ml were collected and assayed by HPLC. Fractions containing the desired compound (242 to 320) were combined, BuOH (2.1 liters) and 1 N HCl (4 ml) was added and the solution was concentrated to 50 ml. The precipitate, which formed by adding Et_2O (300 ml), was collected and dried over KOH pellets and P_2O_5 yielding 2.1 g of the title compound.

Methyl Ester, Hydrochloride (**Va**)

A suspension of T-A3-2** (**II**, 3 g, 1.9 mmol) in 90 ml of 0.35 N HCl gas in abs MeOH was refluxed for 2 hours. The reaction was cooled to 0~5°C and the precipitate was collected and dried under vacuum at room temp obtaining 2.4 g of the crude ester which was suspended in 100 ml of H_2O. The pH was adjusted to 8.3 by adding 0.1 N NaOH, and the cloudy solution was extracted with BuOH (3×200 ml). The organic phase was separated and 200 ml of H_2O and 100 ml of EtOAc was added. The organic layer was separated and concentrated to 200 ml. By adding 200 ml of Et_2O a solid separated which was filtered off, washed with Et_2O and suspended in 50 ml of abs MeOH. The mixture was refluxed for 30 minutes then filtered hot. The filtrate was cooled to 15°C, 1.6 ml of 10 M HCl in abs MeOH was added. On standing overnight at room temp a solid separated which was collected and washed with a mixture of Et_2O - Me_2CO (3 : 1) yielding 1.9 g of the title compound.

Ethyl Ester, Hydrochloride (**Vb**)

A suspension of 3 g of **II** in EtOH containing gaseous HCl was reacted as described for compound **Va** to give 1.8 g of the crude ethyl ester, which was dissolved in 180 ml of H_2O. The pH was

* Composition %: T-A3-1 5.4, factors A1 5.7, A2 30.9, A3 16.8, A4 11.6, A5 13.0; related substances 1.1, H_2O 15.0, BuOH 0.05, NaCl 0.2, Cl^- 0.25.

** *Anal* %: H_2O 8.4, ashes 0.6.

adjusted to 8.9 with 0.1 N NaOH. The resulting suspension was extracted with 300 ml of a mixture of EtOAc - BuOH (2:1). The organic layer was discarded and the aqueous phase was extracted with 2×200 ml of BuOH. This extract was washed with H_2O (60 ml) and concentrated to a final volume of about 200 ml. By adding Et_2O a solid separated which was collected, then suspended in 50 ml of H_2O. To the mixture made clear by adding 0.9 ml of 1 N HCl, 200 ml of BuOH was added. The mixture was concentrated at 50°C under vacuum to a final volume of about 60 ml. By adding Et_2O a solid formed which was filtered and suspended in 100 ml of 3 M gaseous HCl in abs EtOH. The resulting suspension was concentrated to a final volume of about 40 ml, the precipitate was collected, washed with 10 ml of EtOH, then with 200 ml of Et_2O yielding 1.1 g of the title compound.

n-Butyl Ester, Hydrochloride (Ve)

A solution of 3 g of **II** in BuOH containing gaseous HCl was stirred at 60°C (bath temp) for 3 hours, then it was treated as described above. The organic layer was separated and diluted with 200 ml of BuOH. The resulting cloudy solution was washed with 200 ml of H_2O, then concentrated to a final volume of about 80 ml. By adding 100 ml of EtOAc a solid separated which was collected and suspended in 250 ml of H_2O. After stirring for 30 minutes, 30 ml of MeOH and 2 ml of 1 N HCl was added. The resulting clear solution was brought to pH 8.1 with 0.1 N NaOH and extracted with EtOAc (400 ml). The organic layer was discarded and the aqueous layer was extracted with 2×200 ml of BuOH. 1 N HCl (2 ml) was added to the organic layer and the resulting solution was concentrated to about 40 ml. By adding 120 ml of Et_2O a solid separated which was filtered off obtaining 0.98 g of the title compound.

2-Chloroethyl Ester, Hydrochloride (Vc)

A stirred suspension of 1.4 g (0.9 mmol) of **II** in 20 ml of 2-chloroethanol was treated with 1 ml of $SOCl_2$ at −10°C. The reaction mixture was allowed to warm at room temp and stirred for one day. After cooling to −10°C, additional $SOCl_2$ (1 ml) was added, and stirring at room temp was continued for one day. By pouring the reaction mixture into Et_2O (200 ml) 1.2 g of the crude compound was obtained which was purified as described for compound **Vb**, giving 0.25 g of the title compound.

N-BOC-T-A3-2 (IV)

2,4,5-Trichlorophenyl-*tert*-butylcarbonate (1 g, 3.3 mmol) and triethyllamine (TEA) (2.1 ml) was added to a stirred solution of 3.8 g (2.4 mmol) of **II** in 60 ml of distilled DMF. The mixture was kept for 48 hours at room temp, then it was diluted with 240 ml of H_2O and the pH was adjusted to 4 with 1 N HCl. The reaction mixture was extracted with BuOH (300 ml). The organic phase was separated, washed with 40 ml of H_2O and concentrated. Et_2O (300 ml) was added. After cooling overnight a solid formed which was filtered off to yield 3.2 g of the title compound.

Benzyl Ester, Trifluoroacetate (Vg)

A solution of 0.5 g (0.33 mmol) of **IV**, 50 mg (0.5 mmol) of $KHCO_3$ and 0.08 ml (0.66 mmol) of benzyl bromide in 7 ml of distilled DMF was stirred at room temp for 24 hours. After diluting with 60 ml of H_2O, the pH was brought to 5 with AcOH and the reaction product was extracted with 2× 50 ml of a mixture EtOAc - BuOH (2:1). The organic layer was separated, washed with 30 ml of H_2O and concentrated to 10 ml. By adding Et_2O (100 ml) 0.45 g of *N*-BOC-T-A3-2 benzyl ester suitable for the next step was obtained (retention time (t_R) 36.5 minutes). This intermediate was dissolved in 2.5 ml of TFA, and the reaction mixture was stirred at room temp for 15 minutes. After diluting with Et_2O (100 ml) 0.4 g of **Vg** was obtained.

4-Methylbenzyl Ester (Vh)

A solution of 0.5 g of **IV**, 50 mg of $KHCO_3$ and 0.09 ml (0.66 mmol) of 4-methylbenzyl chloride in 7 ml of DMF was stirred overnight at room temp, then an additional amount of 4-methylbenzyl chloride (0.09 ml) and $KHCO_3$ (20 mg) was added. The reaction mixture was stirred at 50°C for 7 hours, then it was washed up as described for **Vg**, obtaining 0.48 g of *N*-BOC-T-A3-2 4-methylbenzyl ester (t_R 40.1 minutes) which was dissolved in 2.5 ml of TFA. The reaction mixture was stirred for 15 minutes at room temp, Et_2O (100 ml) was added and the precipitate was collected.

The crude material (0.48 g) was then purified by flash chromatography on a column packed with 70 g of Silica gel RP-8 developed with a linear gradient from 25 to 50% of CH_3CN in H_2O. The fractions containing compound **Vh** were combined on the bases of HPLC, BuOH was added and the solvents were evaporated to dryness. The residue was triturated with Et_2O and filtered off giving 0.15 g of the title compound.

2-Hydroxyethyl Ester, Trifluoroacetate (**Vd**)

A solution of 0.5 g of **IV**, 50 mg of $KHCO_3$ and 50 μl (0.66 mmol) of 2-bromoethanol in 7 ml of DMF was stirred at room temp while a total of 75 mg of $KHCO_3$ and 0.18 ml of 2-bromoethanol was added over 98 hours. The reaction mixture was worked up as described for **Vg** obtaining 0.45 g of the *N*-BOC-T-A3-2 2-hydroxyethyl ester (t_R 25.7 minutes) which was dissolved in 2.5 ml of TFA and treated as for **Vg**. Pure compound **Vd** was obtained, 0.39 g.

Esters of Deglucoteicoplanin (**III**)

4-Chlorobutyl Ester (**VIIIh**)

A suspension of teicoplanin (**I**, 10 g, 4.4 mmol) in 400 ml of anhydrous THF was heated at 45~50°C while bubbling gaseous HCl continuously for 36 hours. The resulting solution was concentrated to a small volume, Et_2O was added and the precipitate which formed was collected, washed with Et_2O and re-dissolved in 1 liter of a mixture CH_3CN - H_2O (1:4). The solution was applied to a column containing 0.6 kg of silanized silica gel in 0.2% aq $HCOONH_4$. The column was developed with a linear gradient from 30 to 90% CH_3CN in H_2O at a rate of 300 ml/hour, collecting 20 ml fractions. Fractions containing the derived compound were combined and worked up yielding 3.2 g of **VIIIh**.

n-Butyl Ester, Hydrochloride (**VIIIg**)

Butanolic 6.5 N HCl (4.5 ml) was added with stirring to a suspension of 1.75 g (1.1 mmol) of T-A3-2 (**II**) in 56 ml of BuOH. By heating at 60~65°C for 12 hours a solution was obtained which was concentrated to 30 ml. After adding 200 ml of H_2O the mixture was extracted with EtOAc (200 ml). The organic layer was separated, butanolic 1 N HCl was added (1.2 ml) and the solution was concentrated to 20 ml. By adding a mixture of Et_2O - Me_2CO (3:1) a solid separated which was collected yielding 0.93 g of the title compound.

3-Hydroxybutyl Ester (**VIIIi**)

Dry HCl (0.2 g) was absorbed by bubbling into a solution of 0.5 g (0.3 mmol) of **II** in 15 ml of 1,3-butanediol. The reaction mixture was heated at 60°C for 50 hours, then it was cooled and poured into 50 ml of H_2O. The pH was brought to 5 by adding Na_2CO_3. A precipitate separated which was filtered off and washed with H_2O obtaining 0.2 g of crude ester. The filtrate was extracted with BuOH. By evaporation to dryness of the organic extracts a residue was obtained, which was triturated with Et_2O and collected (0.27 g). The two crops were combined, dissolved in 10 ml of 50% aq CH_3CN, Silica gel RP-8 was added (0.5 g) and the solvents were evaporated to dryness. The residue was loaded at the top of a column containing 60 g of the same silica gel in a mixture 0.02 M $HCOONH_4$ - CH_3CN (85:15). The column was developed with a gradient from 15 to 40% of CH_3CN in H_2O. The fractions containing the desired compound were combined and worked up as usual giving 0.11 g of **VIIIi**.

n-Octyl Ester, Hydrochloride (**VIIIl**)

A suspension of 0.93 g (0.6 mmol) of **II** in 180 ml of 1 N octanolic HCl was stirred at 70°C for 10 hours. The clear solution was cooled to 15°C and 800 ml of Et_2O was added. The solid which separated was collected yielding 0.72 g of the crude ester which was dissolved in 60 ml of a mixture of MeOH - H_2O (8:1). After adding 400 ml of H_2O and 1 ml of 1 N HCl the mixture was extracted with EtOAc (2×400 ml). The extracts were combined and 1 ml of 1 N HCl in 100 ml of BuOH was added. The solution was concentrated to 80 ml, and 100 ml of a mixture EtOAc - Et_2O (3:2) was added. The resulting cloudy solution was kept at 10°C for 3 days. A solid separated which was collected, yielding 0.16 g of **VIIIl**.

Benzyl Ester, Hydrochloride (**VIIIn**)

A suspension of 18 g (11.7 mmol) of **II** in 600 ml of 1 N HCl in benzyl alcohol was stirred at 60°C

for 3 hours. The solution which formed was cooled to 15°C and 4 liters of a mixture of Et_2O - hexane (4 : 3) was added. A solid separated which was filtered off, washed with Et_2O (1 liter) and re-dissolved in 150 ml of MeOH. The solution was diluted with 1 liter of H_2O and extracted twice with 2 liters of EtOAc. The organic layers were combined, 10 ml of 1 N HCl and 200 ml of BuOH were added and the solution was concentrated to a small volume. By adding 1 liter of a mixture Et_2O - hexane (3 : 2) a solid separated which was collected yielding 8.5 g of the ester (HPLC titer 70%, H_2O and solvents 15%, undefined impurities 15%). Purification by Silica gel RP-8 chromatography as previously described gave 3.8 g of the title compound.

2-Methoxyethyl Ester (**VIIIf**)

A solution of 0.5 g (0.36 mmol) of deglucoteicoplanin* (**III**) in 500 ml of 2-methoxyethanol containing 1 ml of concd H_2SO_4 and 3 g of Molecular sieves 3A (8~12 mesh, BDH) was heated at 80°C for 10 hours. After filtering, the solution was brought to neutrality with $NaHCO_3$, then the solvent was evaporated to dryness. The residue was dissolved in 10 ml of 50% aq MeOH and Silica gel RP-8 (0.5 g) was added. The solvents were evaporated to dryness and the residue was loaded at the top of a column containing 250 g of the same silica gel slurried in 10% aq CH_3CN. The column was developed with a gradient from 10 to 50% of CH_3CN in H_2O. By working out the fractions containing the ester as previously described 70 mg of **VIIIf** was obtained.

N-CBZ-deglucoteicoplanin (**VI**)

A solution of 0.45 ml (3.1 mmol) of benzylchloroformate in 10 ml of Me_2CO was added dropwise to a stirred solution of 2.5 g (1.8 mmol) of **III** and 0.5 g (5.9 mmol) of $NaHCO_3$ in 150 ml of a mixture Me_2CO - H_2O (2 : 1) at 0~3°C. After 30 minutes the reaction mixture was diluted with 500 ml of H_2O and extracted with 500 ml of Et_2O. The aqueous phase was separated, adjusted to pH 3.5 with 1 N HCl and extracted with 600 ml of a mixture BuOH - EtOAc (1 : 2). The organic layer was separated, washed with 200 ml of H_2O and then concentrated to a small volume. By adding Et_2O a solid separated which was filtered off, washed with Et_2O and dried yielding 2.1 g of the title compound.

N-CBZ-deglucoteicoplanin Ethyl Ester (**VIb**)

Ethyl bromide (0.2 ml, 2.7 mmol) was added with stirring to a solution of 1 g of **VI** (0.7 mmol) and 70 mg (0.5 mmol) of powdered K_2CO_3 in 30 ml of DMF. The reaction mixture was stirred at room temp overnight, then it was poured into 500 ml of H_2O and the pH was brought to 8 with K_2CO_3. The reaction mixture was extracted with EtOAc (3×300 ml) and the organic extracts were combined, washed with Et_2O and concentrated to dryness. The residue was dissolved in EtOAc (50 ml). By adding Et_2O a precipitate formed which was filtered off giving 0.8 g of **VIb**.

Ethyl Ester (**VIIIb**)

Compound **VIb** (0.54 mg) was dissolved in 5 ml of EtOH and 5%-Pd on carbon (50 mg) was added. Hydrogen was bubbled in the mixture with stirring at room temp and atmospheric pressure. The catalyst was filtered off, washed with EtOH, and Et_2O (200 ml) was added to the filtrate. A solid separated which was collected obtaining 0.45 mg of the title compound.

N-CBZ-deglucoteicoplanin, 2-Fluoroethyl Ester (**VIc**)

To a solution of 1.5 g (1.05 mmol) of **VI** in 50 ml of DMF, K_2CO_3 (0.15 g, 1 mmol) and 1-bromo-2-fluoroethane (0.2 ml, 2.6 mmol) were successively added. The mixture was stirred at room temp for 48 hours, then it was poured into a mixture Et_2O - hexane (2 : 1). The precipitate was filtered off yielding 1.75 g of crude material which was dissolved in a few milliliters of MeOH and poured into 500 ml of EtOAc. The solution was washed with 500 ml of H_2O containing $NaHCO_3$ (1 g) and NaCl (5 g), then with H_2O. To the organic phase BuOH was added (100 ml), then it was concentrated to 20 ml. By adding Et_2O a solid separated which was collected (1 g). This compound was dissolved in 50 ml of 35% aq CH_3CN and chromatographed on a column containing 250 g of silanized silica gel slurried with 35% CH_2CN in H_2O. The column was developed with 4 liters of linear gradient from 35 to 55% of CH_3CN in H_2O, collecting 20 ml fractions. The fractions containing the desired com-

* *Anal* %: H_2O 10.5, solvents 3.0.

pound were combined, BuOH was added and the solvents were evaporated to dryness. The residue was triturated with Et_2O and collected yielding 0.5 g of the title compound.

2-Fluoroethyl Ester (**VIIIc**)

5%-Pd on $BaSO_4$ (0.4 g) was added to a solution of 0.4 g of **VIc** in 50 ml of a mixture of 0.1 N HCl - MeOH (3 : 7) and hydrogenated at room temp and ambient pressure during 2 hours. The catalyst was filtered off and washed with 50 ml of MeOH. Silanized silica gel (5 g) was added to the filtrate with stirring, then the solvent was evaporated under vacuum and the residue was loaded on the top of a column containing 50 g of the same silica gel prepared with a solution of 5% CH_3CN in H_2O brought to pH 3 with 10% HCl. The column was eluted with a linear gradient from 5 to 25% of CH_3CN in H_2O at pH 3 collecting 20 ml fractions. Fractions containing the desired compound (fractions 36~70) were combined, BuOH was added and the solvents were evaporated to dryness. The residue was triturated with Et_2O and filtered off, yielding 50 mg of the title compound.

N-CBZ-deglucoteicoplanin 2-Bromoethyl Ester (**VId**)

It was prepared from 1.5 g of **VI** and 1 ml (11.5 mmol) of 1,2-dibromoethane as described for **IVc**, except that the reaction mixture was dripped into 900 ml of Et_2O. After purification 1.2 g of the title compound was obtained.

2-Bromoethyl Ester, Hydrochloride (**VIIId**)

A solution of 1 g of **VId** in a mixture of 1 N HCl - MeOH (1 : 3) was hydrogenated at room temp and ambient pressure in the presence of 1 g of 5%-Pd on $BaSO_4$. After 3 hours the reaction mixture was filtered from the catalyst, silanized silica gel (10 g) was added to the filtrate and the solvent was evaporated under vacuum. The residue was loaded on the top of a column containing 250 mg of the same silica gel in a mixture CH_3CN - H_2O (1 : 3). The column was eluted with a linear gradient from 25 to 70% of CH_3CN in H_2O, collecting 20 ml fractions. Fractions containing the desired compound were combined, BuOH was added and the solvents were evaporated to dryness. The residue was triturated with Et_2O, yield 0.1 g of **VIIId**.

N-CBZ-deglucoteicoplanin Pivaloyloxymethyl Ester (**VIm**)

To a stirred solution of 0.7 g (0.47 mmol) of **VI** in 20 ml of DMF, 0.1 ml (0.7 mmol) of TEA, 0.1 ml (0.7 mmol) of chloromethylpivalate and 35 mg (0.2 mmol) of NaI were added. The reaction mixture was heated at 45°C for 4 hours, then additional 0.1 ml of TEA and 0.15 ml of chloromethylpivalate was added. Heating was maintained for 4 hours then the same amount of these reagents was added. After stirring for 24 hours at room temp, 400 ml of Et_2O was added. The oily material which separated was collected and treated with 200 ml of a mixture Me_2CO - Et_2O (1 : 9). The solid which formed was filtered off and washed with Et_2O yielding 0.7 g of the title compound suitable for the further reaction. An analytical sample was obtained by silica gel chromatography with a linear gradient of CH_2Cl_2 - MeOH from 95 : 5 to 50 : 50.

Pivaloyloxymethyl Ester, Hydrochloride (**VIIIm**)

A solution of 1.6 g (0.9 mmol) of **VIm** in 400 ml of MeOH was hydrogenated as previously described in the presence of 1.2 g of 5%-Pd on carbon. After 30 minutes the reaction was completed, the catalyst was filtered off and washed with 600 ml of a mixture of 0.1 N HCl - MeOH (1 : 4). BuOH (400 ml) was added to the combined filtrate and washing and the mixture was concentrated to a small volume. By adding Et_2O a solid separated which was collected (1.33 g) then dissolved in 100 ml of a mixture CH_3CN - MeOH (85 : 15) and applied to a column of 300 g of silica gel in CH_3CN. The column was developed with 500 ml each of the following solvent mixtures: CH_3CN - MeOH (90 : 10); (85 : 15); (80 : 20); (75 : 25); (70 : 30); (65 : 35). Fractions of 150 ml each were collected. Fractions 14 to 19 were pooled. 0.05 N butanolic HCl was added and the mixture was concentrated to a final volume of 150 ml. The solid which separated was collected, yielding 0.44 g of **VIIIm**.

N-BOC-Deglucoteicoplanin (**VII**)

2,4,5-Trichlorophenyl-*tert*-butylcarbonate (2 g, 6.7 mmol) and 2 ml of TEA (14.3 mmol) was added to a stirred solution of 5.5 g (4 mmol) of **III** in 100 ml of DMF. The reaction mixture was

kept at room temp for 24 hours then it was poured into 1 liter of Et_2O. The precipitate was collected, washed with Et_2O (8 g) and dissolved in a little amount of MeOH. After diluting with H_2O (1 liter) the solution was brought to pH 2.5 with 10% HCl and extracted with 1 liter of EtOAc then with 1 liter of EtOAc containing 10% of BuOH. The organic extracts were combined and concentrated to a small volume. By adding Et_2O a precipitate formed which was filtered off (5.2 g).

Methyl Ester, Trifluoroacetate (**VIIIa**)

A finely ground portion of $KHCO_3$ (40 mg, 0.4 mmol) and CH_3I (30 μl, 0.48 mmol) were added to a stirred solution of **VII** (0.5 g, 0.36 mmol) in 10 ml of DMF. The reaction mixture was stirred at room temp for 3 hours, then H_2O (100 ml) was added and extracted with BuOH (3×100 ml). The organic extracts were washed with H_2O and concentrated to 20 ml. The reaction product was precipitated by adding Et_2O (200 ml). After standing overnight at 0°C, the product was collected, yielding 0.32 g of the intermediate *N*-BOC-deglucoteicoplanin methyl ester (**VIIa**) (t_R 21.9 minutes)* which was suspended with stirring in 3 ml of TFA. After 30 minutes the solid dissolved. Et_2O (50 ml) was added and the precipitate was collected obtaining 0.25 g of **VIIIa**.

2-Hydroxyethyl Ester, Trifluoroacetate (**VIIIe**)

$KHCO_3$ (0.1 g, 1 mmol) and 2-bromoethanol (0.02 ml, 0.34 mmol) were successively added with stirring to a solution of **VII** (0.45 g, 0.3 mmol) in 5 ml of DMF. After 18 hours at room temp additional $KHCO_3$ (50 mg) was added then the reaction mixture was kept at 50°C for 4 hours. After cooling the mixture was diluted with H_2O (60 ml), the pH was brought to 2 with 1 N HCl and the solution was extracted with BuOH (2×50 ml). The organic extracts were washed with H_2O and concentrated to dryness. The residue was dissolved with MeOH (1 ml). By adding Et_2O (100 ml) a precipitate formed which was filtered off, washed with Et_2O and dried in the air yielding 0.45 mg of the crude intermediate *N*-BOC-deglucoteicoplanin 2-hydroxyethyl ester (**VIIe**).

This product was purified by flash chromatography on 60 g of Silica gel RP-8 slurried in a mixture of H_2O - CH_3CN (9:1). The column was developed with a linear gradient from 10 to 40% of CH_3CN in H_2O, collecting 15 ml fractions. Fractions containing the desired compound were pooled, BuOH added and evaporated to dryness. The residue was triturated with Et_2O and filtered obtaining 0.19 mg of pure *N*-BOC ester, which was suspended in 1 ml of CH_2Cl_2. TFA (1 ml) was added with stirring. After 10 minutes the solvents were evaporated and the residue was triturated with Et_2O and filtered. Yield 0.155 mg of the title compound.

2-(*N*-Morpholinyl)ethyl Ester, Bis-trifluoroacetate (**VIIIo**)

A solution of 0.45 g (0.3 mmol) of **VII**, 0.13 g (1.3 mmol) of $KHCO_3$ and 0.12 g (0.66 mmol) of 4-(2-chloroethyl)morpholine hydrochloride was made stepwise in 4 ml of DMF. The solution was stirred at room temp for 50 hours then additional 60 mg of the reagent and 30 mg of $KHCO_3$ was added. After stirring for 15 hours, the reaction mixture was diluted with 30 ml of H_2O and extracted with BuOH (2×50 ml). The organic layers were separated and evaporated to dryness. The residue was triturated with Et_2O and filtered off, yielding 0.45 g of crude material which was purified by flash chromatography on 100 g of silica gel, eluting with a mixture of CH_2Cl_2 - MeOH - 37% NH_4OH (80:20:1). By working up as previously described the fractions containing the *N*-BOC-deglucoteicoplanin 2-(*N*-morpholinyl)ethyl ester (**VIIo**) 0.15 g of pure compound was obtained. Treatment with TFA as reported for **VIIa**, yielded 0.15 g of the title compound.

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* HPLC with the same chromatograph and solvent mixtures described in the Experimental section. Column Hibar LiChrosorb RP-18 (250 mm, 7 μm). Flow rate 1.5 ml/minute. Gradient as follows:

Minutes	0	5	10	20	30.
% B	10	10	30	60	80.

t_R of compound **VIIa**: 15.1 minutes.

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