SYNTHESES OF 23-DEOXY-23-*N*-ETHYL-23-(2-FLUORO-, 2,2-DIFLUORO-, AND 2,2,2-TRIFLUOROETHYL)AMINO DERIVATIVES OF MYCAMINOSYL TYLONOLIDE AND 4′-DEOXYMYCAMINOSYL TYLONOLIDE

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(Received for publication August 31, 1984)

Derivatives of mycaminosyl tylonolide (**1**) and 4′-deoxymycaminosyl tylonolide (**2**) containing *N*-ethyl-2-fluoro-, 2,2-difluoro- and 2,2,2-trifluoroethylamino groups at their C-23 have been prepared by treating 23-deoxy-23-ethylaminomycaminosyl tylonolide diethyl acetal (**14**) and its 4′-deoxy analog **15** with 2-fluoro-, 2,2-difluoro- and 2,2,2-trifluoroethyl trifluoromethanesulfonates. The relationship between the antibacterial activity and the numbers of the fluorine atoms introduced in the final products is discussed.

23-Dialkylamino-23-deoxymycaminosyl tylonolides and their 4′-deoxy analogs[1] were found to show strong antibacterial activities against Gram-negative as well as Gram-positive bacteria. This remarkable extension of antibacterial spectrum may be due to the presence of a new basic nitrogen at C-23. This paper describes the effect on the antibacterial activity by conversion of the 23-diethylamino group of 23-deoxy-23-diethylaminomycaminosyl tylonolide (**3**) and its 4′-deoxy analog **4** into fluorine-containing diethylamino groups. Since fluorine is the most strongly electron-withdrawing atom with only slight increase in atomic volume in comparison to that of hydrogen, the replacement of one of the ethyl groups of the 23-diethylamino group of the compounds **3** and **4** with a fluorine-containing ethyl group will decrease the basicity of the nitrogen atoms at C-23 in comparison to that of **3** and **4** without significant change in the group volume at C-23. Thus, such fluorine-containing compounds are of interest to the study of the basicity (at C-23)-activity relationship.

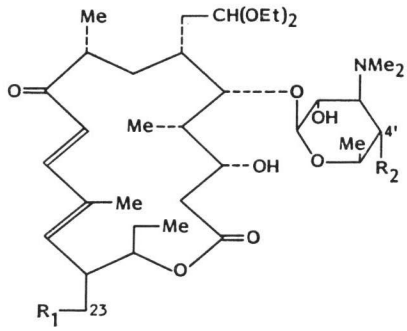
We commenced the experiment to prepare 23-deoxy-23-*N*-ethyl-23-(2,2,2-trifluoroethylamino)-mycaminosyl tylonolide diethyl acetal (**22**) by treating 23-deoxy-23-iodomycaminosyl tylonolide diethyl acetal[2] (**12**) with *N*-ethyl-2,2,2-trifluoroethylamine (**8**), a procedure being routinely used[1] in the syntheses of 23-dialkylamino-23-deoxy derivatives of mycaminosyl tylonolide (**1**) and its 4′-deoxy analog **2**. The reagent **8** was prepared by reduction of *N*-ethyltrifluoroacetamide (**7**) according to KANO *et al.*[3]

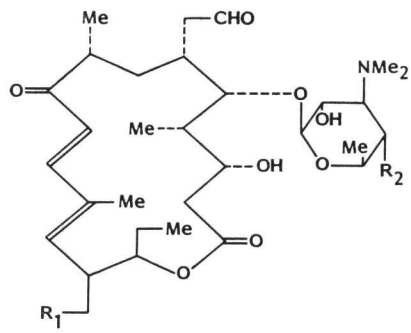
$$EtNH_2 \rightarrow Et(CRF_2CO)NH \rightarrow Et(CRF_2CH_2)NH$$

R=H **5** R=H **6**
R=F **7** R=F **8**

(**8** could also be prepared from **7** by the action of lithium aluminium hydride in ether in a similar yield). However, the reaction of **8** with **12** did not proceed at all only recovering the starting material **12**. Reaction of **12** with *N*-ethyl-2,2-difluoroethylamine (**6**) was next tried. The reagent **6** was prepared[3] likewise from *N*-ethyldifluoroacetamide (**5**), which in turn, was prepared by coupling ethylamine and

Chart 1.





	R_1	R_2
12	I	OH
13	I	H
14	NHEt	OH
15	NHEt	H
16	$NEt(CH_2CH_2F)$	H
18	$NEt(CH_2CHF_2)$	OH
20	$NEt(CH_2CHF_2)$	H
22	$NEt(CH_2CF_3)$	OH
24	$NEt(CH_2CF_3)$	H

	R_1	R_2
1	OH	OH
2	OH	H
3	NEt_2	OH
4	NEt_2	H
17	$NEt(CH_2CH_2F)$	H
19	$NEt(CH_2CHF_2)$	OH
21	$NEt(CH_2CHF_2)$	H
23	$NEt(CH_2CF_3)$	OH
25	$NEt(CH_2CF_3)$	H

$CH_2FCH_2OH \rightarrow CH_2FCH_2OSO_2CF_3$ **9**
$CHF_2CH_2OH \rightarrow CHF_2CH_2OSO_2CF_3$ **10**
$CF_3CH_2OH \rightarrow CF_3CH_2OSO_2CF_3$ **11**

difluoroacetic acid by use[4] of 2,2′-dibenzothiazolyl disulfide and triphenylphosphine (see Experimental). However, the reagent again did not react with **12**. The lack of reactivity is attributed to the remarkably decreased basicity of the reagents **6** and **8** caused by the fluorine atoms in comparison to diethylamine.

We, therefore, changed the synthetic pathway to attach the fluorine-containing ethyl groups to the nitrogens at C-23 of 23-deoxy-23-ethylaminomycaminosyl tylonolide diethyl acetal (**14**) and its 4′-deoxy analog **15**, both of the acetals being readily prepared from **12** and its 4′-deoxy analog **13** and ethylamine. The *N*-alkylations were carried out by use of 2,2,2-trifluoroethyl trifluoromethanesulfonate[5] (**11**), 2,2-difluoroethyl trifluoromethanesulfonate (**10**), and 2-fluoroethyl trifluoromethanesulfonate (**9**), all of them being prepared from the corresponding fluorine-containing alcohols and trifluoromethanesulfonyl chloride. *N*-(2-Fluoroethyl)-derivatization of **15** with **9** was carried out in the presence of triethylamine in benzene at room temperature to give the 23-*N*-(2-fluoroethyl) derivative (**16**). The *N*-(2,2-difluoroethyl)-derivatizations of **14** and **15** also readily proceeded to give **18** and **20**. However, *N*-(2,2,2-trifluoroethyl)-derivatization of **14** and **15** required a high temperature to give **22** and **24** (120°C for 1 ~ 2 hours in a pressure bottle; an improved procedure was also shown; see Experimental). Acidic hydrolysis of the resulting acetals (**16**, **18**, **20**, **22** and **24**) gave the final products (**17**, **19**, **21**, **23** and **25**).

The antibacterial spectra of the above compounds are shown in Table 1 with those of **3** and **4**. The results show that, against Gram-positive bacteria, there is not much difference in activity among the compounds including **3** and **4**, however, against Gram-negative bacteria and *Pseudomonas*, a significant gradual decrease in activity is observed with increase of the number of fluorine atoms. Thus, it is revealed that, for the latter group of bacteria, fluorination of the β-position of one of the

Table 1. Antibacterial spectra of the products synthesized, **3** and **4** (μg/ml).

Test organisms*	Compound Substituent at C-23	**3** NEt_2	**19** $NEt(CH_2CHF_2)$	**23** $NEt(CH_2CF_3)$	**4** NEt_2	**17** $NEt(CH_2CH_2F)$	**21** $NEt(CH_2CHF_2)$	**25** $NEt(CH_2CF_3)$
Staphylococcus aureus 193		0.78	<0.2	0.39	<0.2	0.39	<0.2	<0.2
〃	EMf**	>100	>100	100	12.5	100	100	100
〃	209P	0.78	0.39	0.39	<0.2	<0.2	<0.2	<0.2
〃	MS 9610	>100	>100	>100	>100	>100	>100	>100
Micrococcus luteus PCI 1001		<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Escherichia coli NIHJ		1.56	12.5	50	1.56	6.25	25	12.5
〃 K-12		3.12	25	50	3.12	6.25	12.5	12.5
〃 〃	ML 1629	6.25	>100	>100	3.12	12.5	50	100
〃 〃	ML 1410 R81	12.5	>100	>100	6.25	25	100	100
〃 〃	LA 290 R55	3.12	3.12	6.25	0.78	1.56	3.12	6.25
Klebsiella pneumoniae PCI 602		1.56	6.25	6.25	1.56	1.56	3.12	3.12
Salmonella enteritidis 1891		3.12	3.12	6.25	0.78	1.56	3.12	3.12
S. typhi T-63		3.12	50	>100	3.12	12.5	50	100
Proteus vulgaris OX-19		1.56	50	50	1.56	6.25	25	25
P. aeruginosa A3		12.5	25	50	12.5	50	50	50

* Agar dilution streak method (nutrient agar 37°C, 17 hours).

** Erythromycin-resistant strain.

diethylamino groups of **3** and **4** causes decrease in the antibacterial activity with decrease in basicity of the nitrogen at C-23.

Experimental

General

^{1}H NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer, or at 250 MHz in the FT mode with a Bruker WM 250 spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. UV spectrum was recorded with a Hitachi 200-10 spectrometer. Melting points were determined with a Kofler block and are uncorrected. Mass spectra were recorded with a Hitachi M-80 spectrometer. Thin-layer chromatography (TLC) were performed on Kieselgel 60 F-254 silica gel with detection by spraying with sulfuric acid, followed by slight heating. Column chromatography was performed on Kieselgel 60, 230~400 mesh (E. Merck).

N-Ethyldifluoroacetamide (**5**)

To a mixture of difluoroacetic acid (7 g), 2,2'-dibenzothiazolyl disulfide (25.4 g), and triphenylphosphine (20 g) in dichloromethane-*N*,*N*-dimethylformamide (1:1, 700 ml) were added 0.95 M ethylamine in acetonitrile (90 ml) and triethylamine (7.7 ml) and the solution was kept at room temp for 5 hours. The solution was washed with aq 2% hydrochloric acid, aq 2% sodium hydroxide, water, dried over sodium sulfate, and concentrated. The residue was distilled (4 Torr., bath temp 120°C) to give a syrup of **5**, 2.72 g (30%) (Ref[6] bp_3 60°C); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH_3CH_2), 3.42 (quintet, 2H, CH_3CH_2NH), 5.91 (t, 1H, $^2J_{H,F}$=55 Hz, CF_2HCO).

N-Ethyl-2,2-difluoroethylamine (**6**)

Compound **5** (2.72 g) was treated with sodium borohydride (2.5 g) and titanium (IV) chloride (6.3 g) similarly as described for **8** to give a liquid of **6**, 0.5 g (21%), bp 40°C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, CH_3CH_2), 2.73 (q, 2H, CH_3CH_2), 2.98 (dt, 2H, CHF_2CH_2), 5.86 (tt, 1H, CHF_2CH_2); $^3J_{H-1,H-2}$ =4 Hz, $^3J_{H-1,F}$=15 Hz, $^2J_{H-2,F}$=57 Hz.

N-Ethyltrifluoroacetamide (**7**)

To an ice-cold solution of trifluoroacetic anhydride (15 g) in dry ether (75 ml) was gently introduced ethylamine gas for 10 minutes. The weakly basic solution was concentrated. The residual syrup was distilled (bp_{15}, bath temp 60°C) to give a syrup of **7**, 8.0 g (80%); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH_3CH_2NH), 3.43 (quintet, 2H, J=7 Hz, CH_3CH_2NH), 6~7 (br, 1H, NH).

N-Ethyl-2,2,2-trifluoroethylamine (**8**)

To a suspension of sodium borohydride (12 g) in dry 1,2-dimethoxyethane (330 ml) was gradually added titanium (IV) chloride (29 g). To the resulting blue solution, a solution of **7** (14.4 g) in 1,2-dimethoxyethane (100 ml) was added, and the mixture was stirred at room temp for 12 hours. Addition of water (1 liter) was followed by aq 28% ammonia (50 ml) and the reaction mixture was extracted with benzene. The extracts combined were treated with 0.5 M hydrochloric acid and the aq acidic layer separated was concentrated. To the concentrate (~15 ml), potassium hydroxide was carefully added and the mixture was distilled under atmospheric pressure to give a liquid of **8**, 3.9 g (30%), bp 66~68°C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J=7 Hz, CH_3CH_2), 2.73 (q, 2H, J=7 Hz, CH_3CH_2), 3.13 (q, 2H, $^3J_{H,F}$=9 Hz, CF_3CH_2).

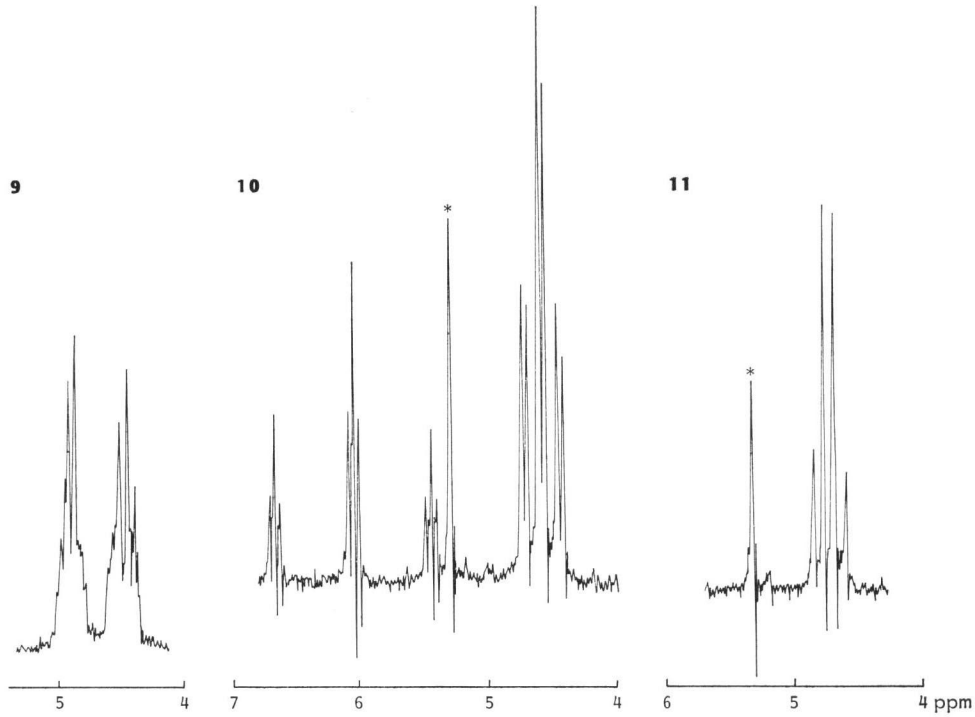
2,2-Difluoroethanol

Prepared from difluoroacetic acid according to HENNE and PELLEY[7], bp 95.5~96°C.

2-Fluoroethyl Trifluoromethanesulfonate (**9**)

To a cold solution (−30°C) of trifluoromethanesulfonyl chloride (15 g) in dichloromethane (15 ml) were added 2-fluoroethanol (2.9 g) and triethylamine (4.6 g), dropwise, in this order, and the mixture was stirred at 0°C for 30 minutes. Cold aq 5% hydrochloric acid was added untill strongly acidic, and the organic layer separated was dried over sodium sulfate. Evaporation followed by distillation (~12 Torr., bath temp 70°C) gave a liquid of **9**, 0.5 g.

Fig. 1. ^{1}H NMR spectra of **9**, **10** and **11** in $CDCl_3$ (* indicates the signals of CH_2Cl_2 contaminated).



2,2-Difluoroethyl Trifluoromethanesulfonate (**10**)

This was prepared from 2,2-difluoroethanol (2 g of the 66% solution in ether), trifluoromethanesulfonyl chloride (5 g) in dichloromethane (5 ml), and triethylamine (3.3 g) in a manner as described for **9**, 1.66 g (42%), bp 104~106°C.

2,2,2-Trifluoroethyl Trifluoromethanesulfonate (**11**)

2,2,2-Trifluoroethanol (3.3 g) was treated trifluoromethanesulfonyl chloride (5 g) and triethylamine (3.3 g) in a manner as described for **9**, and the fraction boiling at 94°C was isolated (3.58 g). The liquid was proved to be a ~85% solution of **11** containing dichloromethane (checked by the ^{1}H NMR spectrum), Ref[5] bp_{740} 89~91°C (prepared from CF_3SO_2F and CF_3CH_2OH).

23-Deoxy-23-ethylaminomycaminosyl Tylonolide Diethyl Acetal (**14**)

To a solution of **12**[2] (110 mg) in dry acetonitrile (2.2 ml) was added 1.55 M ethylamine in acetonitrile (1.1 ml) and the solution was heated at 80°C for 5 hours. Concentration gave a residue, that was dissolved in chloroform, and the solution was washed with satd aq sodium hydrogencarbonate and satd aq sodium sulfate, dried over sodium sulfate and concentrated. Column chromatography of the concentrate with chloroform - methanol - 28% aq ammonia (15: 1: 0.1) gave a solid of **14**, 71.4 mg (73%); $[\alpha]_D^{23}$ +53° (*c* 1, $CHCl_3$); TLC Rf 0.35 (*cf.* **12**, 0.57, with the above solvent system); UV λ_{max}^{MeOH} nm (ε) 281 (22,000); ^{1}H NMR ($CDCl_3$) δ 4.33 (d, 1H, H-1′), 5.70 (d, 1H, H-13), 6.35 (d, 1H, H-10), 7.33 (d, 1H, H-11).

Anal Calcd for $C_{37}H_{66}N_2O_{10}$: C 63.58, H 9.52, N 4.01.
Found: C 63.33, H 9.41, N 3.98.

4′,23-Dideoxy-23-ethylaminomycaminosyl Tylonolide Diethyl Acetal (**15**)

4′,23-Dideoxy-23-iodomycaminosyl tylonolide diethyl acetal[2] (**13**, 4.4 g), was treated in a manner as described for **14** to give a solid of **15**, 2.55 g (66%), $[\alpha]_D^{23}$ +39° (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 4.30 (d, 1H, H-1′), 5.70 (d, 1H, H-13), 6.35 (d, 1H, H-10), 7.32 (d, 1H, H-11).

Anal Calcd for $C_{37}H_{66}N_2O_9 \cdot \frac{1}{2}H_2O$: C 64.25, H 9.70, N 4.05.
Found: C 64.33, H 9.44, N 3.79.

4′,23-Dideoxy-23-(*N*-ethyl-2-fluoroethylamino)mycaminosyl Tylonolide Diethyl Acetal (**16**)

To an ice-cold solution of **15** (78 mg) and triethylamine (28 mg) in dry benzene (0.8 ml) was added 2-fluoroethyl trifluoromethanesulfonate (**9**, 50 mg) and the solution was kept at room temp for 1 hour. Additional triethylamine (56 mg×3) and **9** (100 mg×3) were added in every 1 hour. TLC ($CHCl_3$ - MeOH - 28% aq NH_3, 15: 1: 0.1) of the solution showed two spots at Rf 0.3 (**16**) and 0 (major, 3′-*N*-(2-fluoroethyl)-derivated product?, *cf.* **15**, 0.2). Concentration gave a residue, that was dissolved in chloroform and the solution was washed with satd aq sodium hydrogencarbonate and satd aq sodium sulfate, dried over sodium sulfate, and concentrated. Column chromatography of the residue with $CHCl_3$ - MeOH - 28% aq NH_3, 30: 1: 0.1 gave a solid of **16**, 18 mg (22%).

4′,23-Dideoxy-23-(*N*-ethyl-2-fluoroethylamino)mycaminosyl Tylonolide (**17**)

To a solution of **16** (22.4 mg) in acetonitrile (0.5 ml) was added 0.1 M aq hydrochloric acid (0.85 ml), and the solution was kept at room temp for 1 hour. Neutralization with sodium hydrogencarbonate was followed by extraction with chloroform (0.5 ml×3). The organic solution combined was washed with satd aq sodium sulfate, dried over sodium sulfate, and concentrated. Column chromatography of the residue with $CHCl_3$ - MeOH - 28% aq NH_3, 30: 1: 0.1 gave a solid, that was recrystallized from acetone - hexane to give prisms of **17**, 15 mg (75%), mp 151.5~152°C, $[\alpha]_D^{22}$ +22° (*c* 0.5, $CHCl_3$); MS *m/z* 654 (M, $C_{35}H_{59}FN_2O_8$), 550 [M−104 (=$CH_2NEt(CH_2CH_2F)$], 104; ^1H NMR ($CDCl_3$) δ 4.20 and 4.73 (each t, 2H in total, $^3J_{H,H}$=6 Hz, $^2J_{H,F}$=48 Hz, CH_2FCH_2), 5.80 (d, 1H, H-13), 6.32 (d, 1H, H-10), 7.43 (d, 1H, H-11), 9.85 (s, 1H, CHO).

Anal Calcd for $C_{35}H_{59}FN_2O_8$: C 64.19, H 9.08, N 4.28.
Found: C 64.04, H 9.11, N 4.29.

23-Deoxy-23-(*N*-ethyl-2,2-difluoroethylamino)mycaminosyl Tylonolide (**19**)

A mixture of **14** (63 mg), triethylamine (52 mg), and 2,2-difluoroethyl trifluoromethanesulfonate (**10**, 117 mg of 87.5% solution in dichloromethane) in dry benzene (0.63 ml) was kept at room temp for 4 hours. After addition of chloroform (6 ml), the solution was treated as described for **16**. Column chromatography of the crude product as described for **16** gave a solid of **18**, 59 mg (86%). To the solid in acetonitrile (1.2 ml) was added 0.1 M aq hydrochloric acid (2.3 ml) and the solution was treated as described for **17**. Crude product obtained was recrystallized from acetone - hexane to give **19** as prisms, 49 mg (92%); mp 187~190°C; $[\alpha]_D^{22}$ +16° (*c* 1, $CHCl_3$); MS *m/z* 688 (M, $C_{35}H_{58}F_2N_2O_9$), 565, 174; ^1H NMR ($CDCl_3$) δ 4.75 (dt, 1H, H-15), 5.69 (tt, 1H, $^2J_{H,F}$=57 Hz, $^3J_{H,H}$ =4.5 Hz, CHF_2CH_2), 5.73 (d, 1H, H-13), 6.26 (d, 1H, H-10), 7.32 (d, 1H, H-11), 9.70 (s, 1H, CHO).

Anal Calcd for $C_{35}H_{58}F_2N_2O_9 \cdot \frac{1}{2}H_2O$: C 60.24, H 8.52, N 4.01.
Found: C 60.26, H 8.56, N 4.01.

4′,23-Dideoxy-23-(*N*-ethyl-2,2-difluoroethylamino)mycaminosyl Tylonolide (**21**)

Compound **15** (83 mg) was treated as described for **19** to give **20** (46 mg, 51%). Hydrolysis of **20** as usual gave an amorphous solid of **21**, 38 mg (92%); $[\alpha]_D^{20}$+16° (*c* 1, $CHCl_3$); MS *m/z* 672 (M, $C_{35}H_{58}F_2N_2O_8$), 549, 122; ^1H NMR ($CDCl_3$) δ 4.74 (dt, 1H, H-15), 5.68 (tt, 1H, $^2J_{H,F}$=57.5 Hz, $^3J_{H,H}$ =3.7 Hz, CHF_2CH_2), 5.74 (d, 1H, H-13), 6.30 (d, 1H, H-10), 7.35 (d, 1H, H-11), 9.72 (s, 1H, CHO).

Anal Calcd for $C_{35}H_{58}F_2N_2O_8$: C 62.48, H 8.69, N 4.16.
Found: C 62.23, H 8.56, N 4.15.

23-Deoxy-23-(*N*-ethyl-2,2,2-trifluoroethylamino)mycaminosyl Tylonolide Diethyl Acetal (**22**)

A mixture of **14** (82 mg), triethylamine (0.13 ml), and 2,2,2-trifluoroethyl trifluoromethanesulfonate (**11**, 360 mg of 76% solution in dichloromethane) in dry benzene (0.82 ml) was heated, in a pressure bottle, at 120°C for 2 hours. Concentration gave a residue, that was treated as described for **16** to give, after column chromatography, a solid of **22**. Recrystallization from acetone - cyclohexane gave prisms, 64 mg (70%); mp 161~162°C; $[\alpha]_D^{23}$ +30° (*c* 1, $CHCl_3$).

Anal Calcd for $C_{39}H_{67}F_3N_2O_{10}$: C 59.98, H 8.65, N 3.59.
Found: C 59.74, H 8.65, N 3.38.

23-Deoxy-23-(*N*-ethyl-2,2,2-trifluoroethylamino)mycaminosyl Tylonolide (**23**)

Compound **22** (22 mg) was hydrolyzed as usual to give a solid of **23**, 19 mg (97%). Recrystalliza-

tion gave plates; mp 187~188°C; $[\alpha]_D^{20}$ +13° (*c* 1, $CHCl_3$); MS *m/z* 706 (M, $C_{35}H_{57}F_3N_2O_9$), 565, 516, 140 [$CH_2NEt(CH_2CF_3)$]; ^1H NMR ($CDCl_3$) δ 3.00 (q, 2H, *J*=9 Hz, CF_3CH_2), 4.75 (dt, 1H, H-15), 6.27 (d, 1H, H-10), 7.32 (d, 1H, H-11), 9.71 (s, 1H, H-20).

Anal Calcd for $C_{35}H_{57}F_3N_2O_9$: C 59.47, H 8.13, N 3.96.
Found: C 59.29, H 8.23, N 3.92.

4′,23-Dideoxy-23-(*N*-ethyl-2,2,2-trifluoroethylamino)mycaminosyl Tylonolide Diethyl Acetal (**24**)

Compound **15** (78 mg) was treated as described for **22** (reaction period, 1 hour) to give, after column chromatography, a solid of **24**, 37 mg (42%), and a by-product (24 mg).

Anal Calcd for $C_{39}H_{67}F_3N_2O_9 \cdot \frac{1}{2}H_2O$: C 60.54, H 8.80, N 3.62.
Found: C 60.24, H 8.99, N 3.50.

4′,23-Dideoxy-23-(*N*-ethyl-2,2,2-trifluoroethylamino)mycaminosyl Tylonolide (**25**)

Procedure A: Compound **24** (19 mg) was treated as usual to give a solid of **25**, 13 mg (72%); $[\alpha]_D^{25}$ +15° (*c* 1, $CHCl_3$); MS *m/z* 690 (M, $C_{35}H_{57}F_3N_2O_8$), 549, 140 [$CH_2NEt(CH_2CF_3)$]; ^1H NMR ($CDCl_3$) δ 4.74 (dt, 1H, H-15), 5.72 (d, 1H, H-13), 6.30 (d, 1H, H-10), 7.34 (d, 1H, H-11), 9.72 (s, 1H, H-20).

Anal Calcd for $C_{35}H_{57}F_3N_2O_8$: C 60.85, H 8.32, N 4.05.
Found: C 60.87, H 8.45, N 4.05.

Procedure B: A mixture of **15** (3.73 g), triethylamine (3.6 g), and **11** (11.4 g of 67% solution in dichloromethane) in dry benzene - *N*,*N*-dimethylformamide (1: 1, 19 ml) was heated at 50°C for 3 hours and then worked up as described for **24** and **25** (Procedure A) to give a solid of **25**, 1.67 g (44% based on **15**).

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