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Synthesis of 4′-deoxy-4′-fluoro neamine and 4′-deoxy-4′-fluoro 4′-*epi* neamine†

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The syntheses of 4′-deoxy-4′-fluoro neamine and 4′-deoxy-4′-fluoro 4′-*epi* neamine from the readily available neamine and paromamine are described. Different approaches for the introduction of fluorine such as the use of DAST, sulfonic esters displacement, and epoxide ring opening by fluoride anion were studied. Examples of anchimeric assistance and ring contraction in the aminoglycoside series are highlighted.

Introduction

Aminoglycosides containing the 2-deoxystreptamine unit are important antibiotics agents. Since the discovery of the antibiotic streptomycin, several members of this class of pseudo oligosaccharides have been used in clinical practice.[1] Neomycin which is used topically,[2] and paromomycin widely used in India as an injectable drug against leishmaniasis[3] and against other enteric parasites[4] are among the oldest known (Fig. 1). The common target site of aminoglycosides is found at the decoding center of bacterial 16S ribosomal RNA with the 2-deoxystreptamine ring acting as the anchoring scaffold.[5]

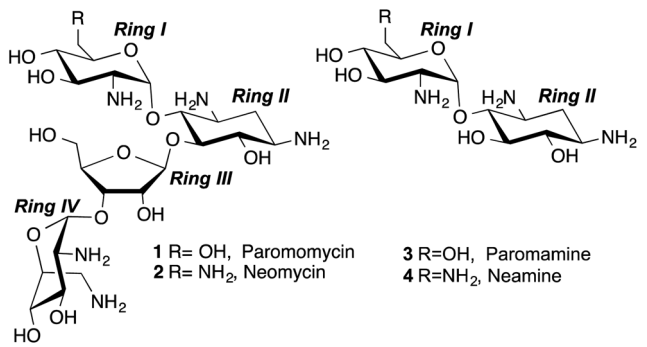

Fig. 1 Structure of the 2-deoxystreptamine (ring II) aminoglycosides paromomycin (**1**) and neomycin (**2**). The aminoglycosides paromamine (**3**) and neamine (**4**) comprise rings I and II of paromomycin and neomycin respectively.

Despite their potent bactericidal activity, the widespread use of aminoglycosides is limited because of dose-dependent nephrotoxicity and ototoxicity.[6] For this reason, their use is limited to intra-hospital environments. The toxicity of aminoglycosides has been linked to the number of amino groups present in the molecule although the mechanism implied is complex and not well understood.[7] For example, the C-4′ deoxygenation of neamine slightly lowered its toxicity when compared to the parental compound, while the tetradeoxy derivative generated a compound having twice the level of toxicity.[8] The replacement of the C-6′ amine by a hydroxyl group in butirosin A reduced the toxicity relative to the parent antibiotic.[8] Likewise, the deoxygenation of kanamycin A in position C-3′ appreciably increases its toxicity.[8] A derivative of neamine bridged with a methylidene group between position C-3′ and C-4′ (NB23) was less toxic than the parental compound.[9] In contrast, the deoxygenated derivative at C-3′ and C-4′ (gentamine C_{1A}) was more toxic, and this effect was directly linked to the basicity of the C-2′ amino group.[9]

Deoxyfluorination of aminoglycoside antibiotics is known to lower toxicity relative to the parent compound, as shown for fluoro derivatives of sporaricin,[10] kanamycin B,[11] and 1-*N*-[(*S*)-4-amino-2-hydroxybutanoyl] derivatives of kanamycin B.[12] The observed lower toxicity was correlated with a diminution in the basicity of the amine group adjacent the fluorine atom.[12,13]

Fluorination of a compound nearby an amino group is well known to diminish the basicity of the amine.[14] This modification also improves metabolic stability, bioavailability, and induces conformational and stereoelectronic changes that could influence the binding of the drug to the receptor.[14a,c]

Herein we report the synthesis of 4′-deoxy-4′-fluoro neamine and 4′-deoxy-4′-fluoro 4′-*epi* neamine by S_N2 displacement reactions of sulfonate esters as well as epoxide opening reactions, intended to be prototypical models for further application to neomycin.[15]

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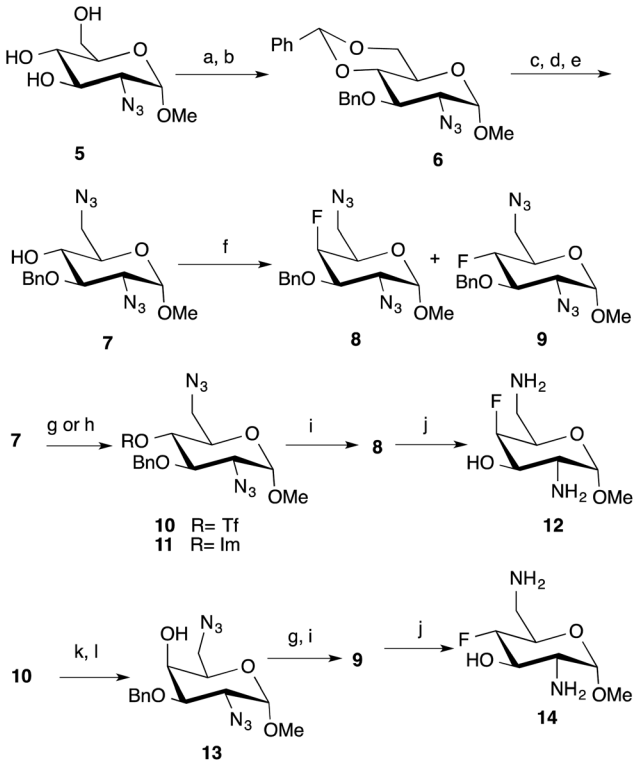


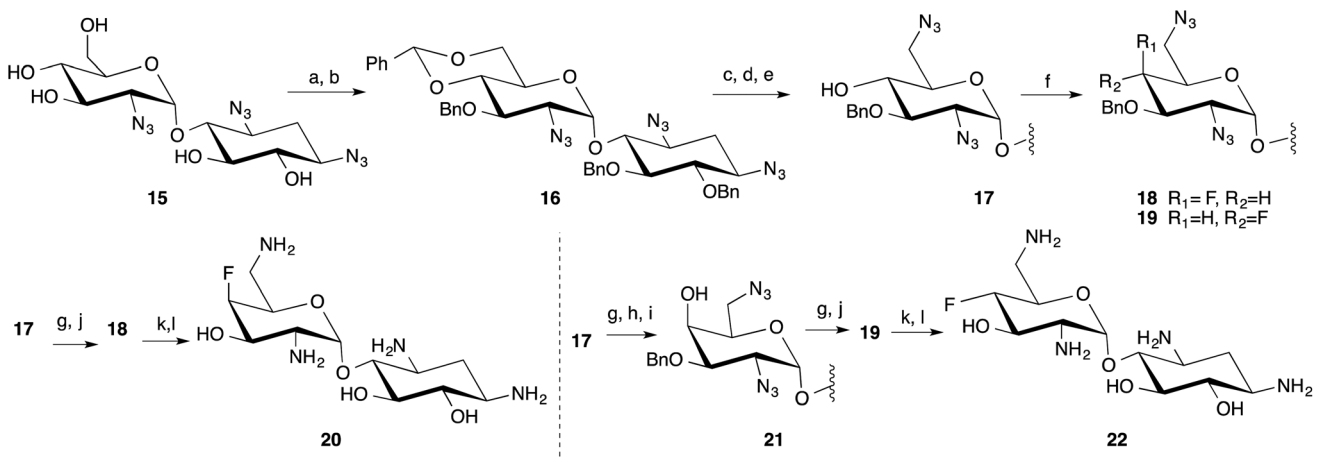
Scheme 1 Reagents and conditions: (a) benzaldehyde dimethylacetal, $(CH_2)_2Cl_2$, CSA, reflux, 2 h, 99%; (b) NaH, BnBr, DMF, room temperature, overnight, 77% (c) AcOH : THF : H_2O 4 : 1 : 1, 60 °C, overnight, 98%; (d) TsCl, pyridine, room temperature, 18 h, 83%; (e) NaN_3, DMF, 70 °C, overnight, 89%; (f) DAST, CH_2Cl_2, room temperature, overnight; (g) Tf_2O, pyridine, 0 °C, 30 min; (h) NaH, DMF, 0 °C, 30 min then 1,1′-sulfonyldiimidazole, −40 °C, 30 min, 90%; (i) TBAF, THF, 60 °C, 2.5 h from **10**: 84%, from **11**: 82%, from **13**: 78%; (j) THF, MeOH, HCl, Pd/C, H_2 (1 atm), for **12**: 77%, for **14**: 70%; (k) TBAAc, THF, 60 °C, 2 h, 76%; (l) MeONa, MeOH, room temperature, quantitative.

Results and discussion

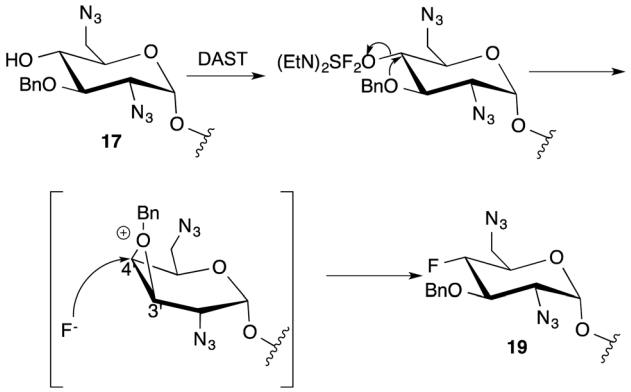
Studies regarding the synthesis of 4′-deoxy-4′,4′-difluoro neamine using per-*N*-Boc protected neamine[16] and previous work done in our laboratory using per-*N*-Cbz aminoglycosides[17] showed that 4′-deoxyfluorination is in general not satisfactory. We therefore decided to use azides as masked amino groups.

We first studied the deoxyfluorination reaction on a model compound that mimics ring I of neamine (**4**). The synthesis started by treatment of **5** (ref. 18) with benzaldehyde dimethylacetal in the presence of 10-camphorsulfonic acid (CSA) followed by benzylation of the free hydroxyl group to afford **6** in a 76% yield (Scheme 1). Cleavage of the benzylidene protecting group under acidic conditions, followed by selective tosylation of the resulting primary hydroxyl and displacement with sodium azide afforded **7** in a 72% overall yield. Treatment of **7** with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 gave a complex mixture from which methyl 2,6-diazido-3-*O*-benzyl-2,4,6-trideoxy-4-fluoro-α-D-galactopyranoside **8** and methyl 2,6-diazido-3-*O*-benzyl-2,4,6-trideoxy-4-fluoro-α-D-glucopyranoside **9** were identified by the characteristic splitting patterns of their fluorine signals in ^{19}F NMR in a 1.1 : 1 ratio respectively. However, the reaction could not be optimized under a variety of conditions and this approach was not pursued further. We then resorted to classical S_N2 displacement reactions of 4-sulfonate esters with fluoride anion.

Reaction of 4-triflate **10** or the imidazylate ester **11** with tetrabutylammonium fluoride (TBAF) afforded **8** as single product in good yield (Scheme 1). The synthesis of the 4-epimeric compound **13** required a double inversion at C-4 of **10** with tetrabutylammonium acetate (TBAAc) followed by deprotection of the resulting acetate with sodium methoxide. The resulting methyl 2,6-diazido-3-*O*-benzyl-2,6-dideoxy-α-D-galactopyranoside **13**, was converted to corresponding triflate, and the latter



Scheme 2 Reagents and conditions: (a) benzaldehyde dimethylacetal, CSA, DCE, reflux, 2 h, 92%; (b) NaH, THF, 0 °C, 1 h, then BnBr, TBAI, room temperature, overnight, 96%; (c) AcOH : H_2O : THF (4 : 1 : 1), 60 °C, overnight, 77%; (d) TsCl, pyridine, CH_2Cl_2, room temperature, overnight, 91%; (e) NaN_3, DMF, 50 °C, overnight, 85%; (f) DAST, CH_2Cl_2, room temperature, overnight, for **18**: 32%, for **19**: 33%; (g) Tf_2O, pyridine, CH_2Cl_2, 0 °C 30 min then room temperature 1 h; (h) TBAAc, THF, 2 h, 60 °C, 79%; (i) MeONa, MeOH, room temperature, overnight, 94%; (j) TBAF, THF, 30 min, 50 °C, for **18**: 82%, for **19**: 66%; (k) PMe_3, NaOH, THF, H_2O, 50 °C, 1 h, 96% from **18**, 94% from **19**; (l) $Pd(OH)_2$/C, MeOH/1 N HCl, H_2 (1 atm), 10 h, for **20**: 91%, for **22**: 90%.



Scheme 3 Plausible mechanism to obtain **19** from **17** using DAST.

was treated with TBAF in THF affording **9** in good yield. Finally, catalytic hydrogenation of **8** and **9** afforded **12** and **14** respectively in reasonable yields.

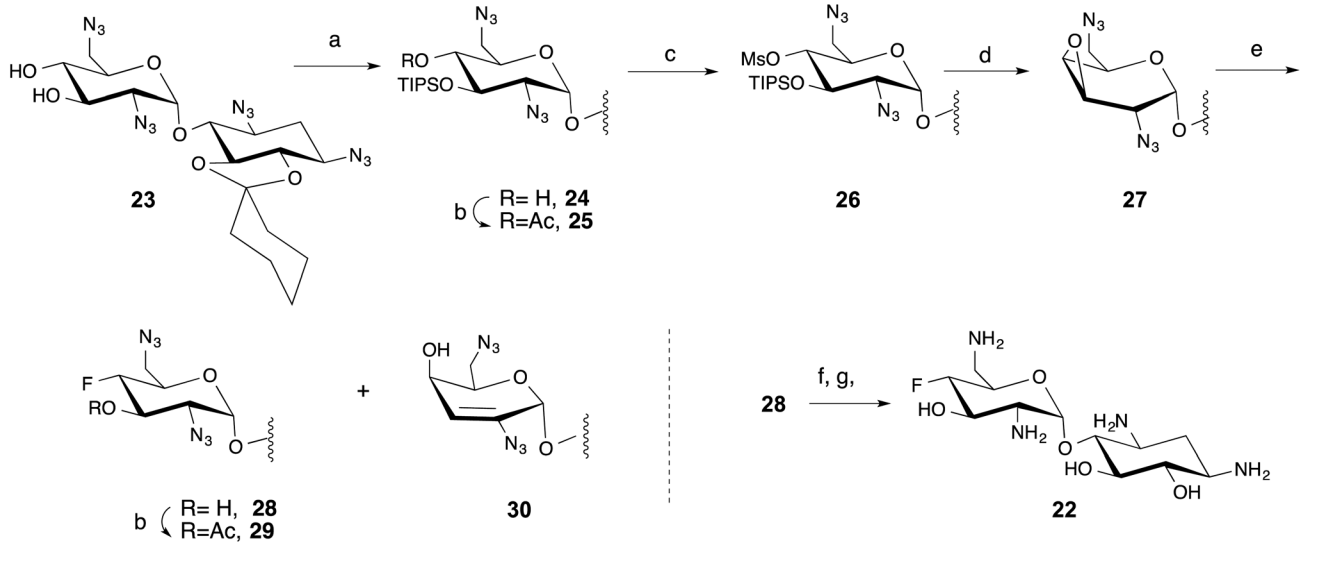
Encouraged by these results, we undertook the synthesis of the 4′-fluorinated derivatives of neamine using two general approaches. In the first approach we used perazido paromamine **15** (Scheme 2) and in the second, perazido neamine as starting materials (Schemes 4 and 5).

We adapted the procedure developed for the synthesis of **7** to the synthesis of 1,3,2′,6′-tetraazido-5,6,3′-tri-*O*-benzyl neamine **17** (Scheme 2). Thus, perazido paromamine **15** (ref. 19) gave **16** in 88% overall yield. The synthesis of **17** was also straightforward and proceeded in a 60% overall yield from **16**. Treatment of **17** with DAST gave two isolable monofluorinated compounds: 1,3,2′,6′-tetraazido-5,6,3′-tri-*O*-benzyl-4′-deoxy-4′-fluoro 4′-*epi* neamine **18** and 1,3,2′,6′-tetraazido-5,6,3′-tri-*O*-benzyl-4′-deoxy-4′-fluoro neamine **19** in a 1 : 1 ratio and 65% yield which were characterized by NMR. The formation of **19** with retention of configuration can be explained by anchimeric assistance of the benzyl group[15f,20] prior to the introduction of the fluorine atom at C-4′ (Scheme 3). In contrast to the results obtained with the monosaccharide model **7**, treatment of **17** with DAST afforded **18** and **19** in reasonable yields although scale-up proved to be challenging. Once again we resorted to the displacement of triflic esters (Scheme 2). Thus, the C-4′ triflate from **17** was reacted with TBAF to afford the deoxyfluoro derivative **18** in good yield. The azido groups were reduced using the Staudinger reduction[21] and the benzyl groups were removed by hydrogenolysis to obtain 4′-deoxy-4′-fluoro 4′-*epi* neamine (**20**) in 38% overall yield from **15**. For the synthesis of the D-gluco-analogue **22** (Scheme 2), the stereocenter at C-4′ in **17** was inverted *via* the displacement of the triflate with TBAAc. Further reaction of the resulting 4′-*epi* acetate with sodium methoxide in methanol afforded **21** in 74% overall yield. The 4′-*epi* alcohol **21** was subjected to the same process as above affording **19** with an overall yield of 66%. Finally, 4′-deoxy-4′-fluoro neamine (**22**) was obtained in 85% yield by reduction of the azide group under

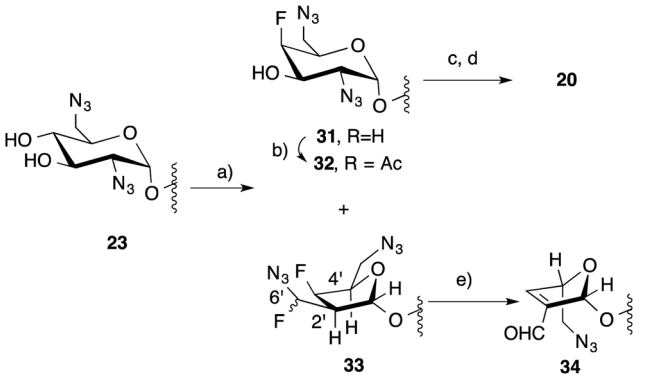
Table 1 Regioselective outcome as a function of solvent and basicity for epoxide **27**

Entry	Reaction conditions[a]	**28**	**30**
1	TBAF, DMF, 50 °C, 3 days	12%	70%
2	TBAF, THF, 50 °C, 3 days	36%	36%
3	TBAF, toluene, 50 °C, 3 days	51%	28%
4	DMF, NaH, 0 °C to room temp, overnight	—	90%

[a] Under the same reaction conditions reported for entries 1, 2 and 3 compound **27** did not react when TBAF was changed by TBACl, TBABr or TBAI.



Scheme 4 Reagents and conditions: (a) TIPSOTf, 2,4,6-collidine, CH_2Cl_2, 0 °C, 15 min, then room temperature, overnight, 68%; (b) Ac_2O, pyridine, room temperature, overnight, for **25**: 52%, for **29**: 43%; (c) MsCl, 2,4,6-collidine, CH_2Cl_2, room temperature, overnight, 68%; (d) TBAF, THF, room temperature, overnight, 76%. (e) TBAF, toluene, 50 °C, 3 days, for **28**: 51%, for **30**: 28%; (f) HCl in MeOH, 0 °C 30 min then room temperature 1 h; (g) PMe_3, NaOH, water, THF, room temperature, overnight then HCl, 68% from **28**.



Scheme 5 Reagents and conditions: (a) DAST, CH_2Cl_2, room temperature, 2 days, for **31**: 34%, for **33**: 22%; (b) Ac_2O, pyridine, 72%; (c) AcOH : dioxane : H_2O, reflux, 18 h; (d) PMe_3 (exc), NaOH, H_2O, THF, room temperature, 2 h, 88% from **31**; (e) PMe_3 (1 equiv.), THF, −78 °C 15 min to room temperature, then aqueous NaOH, room temperature, 2 h, 34%.

Staudinger conditions,[21] and cleavage of the benzyl groups by catalytic hydrogenation in 22% yield from **15**.

We also explored an alternative approach to **20** and **22** starting with the neamine derivative **23** (ref. 9) (Schemes 4 and 5).

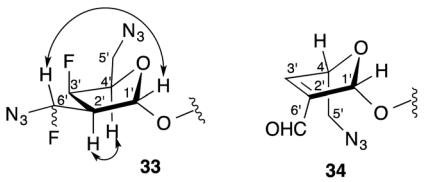
The synthesis of epoxide **27** by selective protection of **23** (ref. 9) with tri-isopropylsilyltriflate (TIPSOTf) afforded **24** in 68% yield. The reaction proceeded with complete regiocontrol affording the 3′ silyl ether selectively. The assignment was confirmed by NMR where a displacement to lower field of C-4′ proton chemical shift was observed in the acetate **25** as compared with the shift observed for C-4′ proton in the case of **24** (Table 3).

Treatment of **24** with methanesulfonyl chloride afforded **26**. As expected, the cleavage of the silyl moiety of **26** with TBAF was followed by the internal displacement of the 3′-*O*-mesyl group affording **27** in moderate yield. Opening of the epoxide with TBAF led to the intended 4′-deoxy-4′-fluoro neamine derivative **28** (51% yield). However, the vinyl azide **30** was also formed as a significant by-product (28% yield). The ratio of **28** to **30** in the epoxide ring opening reaction varied with the solvent (Table 1). The best result for fluorination was obtained in toluene. Treatment of **27** with base gave vinyl azide **30** as a sole product in excellent yield (Table 1 entry 4). Vinyl azides in the carbohydrate series resulting from β-elimination are rare.[22]

Removal of the cyclohexylidene acetal in **28** under acidic conditions, followed by reduction of the azide groups as described above afforded 4′-deoxy-4′-fluoro neamine **22** in 68% yield (14% overall from **23**) (Scheme 2).

The synthesis of 4′-deoxy-4′-fluoro 4′-*epi* neamine starting from neamine derivative **23** was accomplished as shown in Scheme 5. Treatment of **23** (ref. 9) with DAST in CH_2Cl_2 at room temperature for 2 days afforded the mono fluoro derivative **31** (34%), and the ring contracted difluorinated compound **33** (22%) (Scheme 5). The deoxyfluorination at C-4′ on **23** with DAST proceeded with inversion of configuration, as evidenced by NMR analysis of the acetylated derivative **32** (Table 3).

Table 2 Observed NOE interactions, chemical shift assignment, and coupling constants for contracted ring compound **33** and **34**

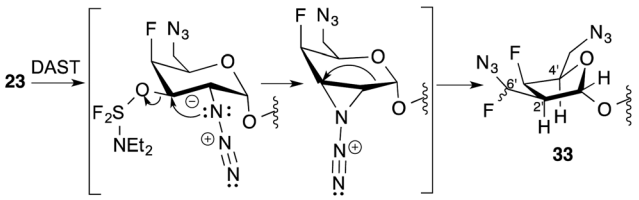


	δ/ppm		J/Hz			J/Hz	
Proton[d]	**33**[a]	**34**[b]		**33**[a]	**34**[b]		**33**[a,c]
H-1′	5.65	7.00	$J_{1',2'}$	4.4	—	$J_{1',F6'}$	1.8
H-2′	2.75	—	$J_{2',3'}$	4.4	—	$J_{2',F6'}$	11.0
H-3′	5.19	6.51	$J_{3',4'}$	2.1	3.4	$J_{6',F6'}$	54.1
H-4′	4.41	5.34	$J_{4',5a'}$	6.6	4.5	$J_{2',F3'}$	28.6
H-5a′	3.56	3.41	$J_{4',5b'}$	6.6	4.5	$J_{3',F3'}$	53.3
H-5b′	3.65	3.65					
H-6′	5.70	9.81	$J_{5a',5b'}$	12.7	13.2	$J_{4',F3'}$	28.1

[a] 300 MHz, $CDCl_3$. [b] 400 MHz, $CDCl_3$; $^4J_{1',4'} = 1.5$ Hz (*W* coupling), $^4J_{1',3'} = 0.7$ Hz (allylic coupling). [c] J_{H-F} coupling constants measured in proton spectra. [d] For other protons see experimental procedures and Table S1 in ESI.

Removal of protecting groups in **31** afforded 4′-deoxy-4′-fluoro 4′-*epi* neamine (**20**) (30% overall from **23**). This is amenable to scale-up and the short number of steps compensates for the low yield observed in the fluorination step (Scheme 5).

Treatment of **23** with DAST for longer reaction times afforded ring-contracted product **33** as the major product (Scheme 5). Ring contraction had proceeded with retention of configuration at C-2′ as evidenced by NMR analysis and by a NOE interaction between C-2′ proton and C-4′ proton (Table 2). This stereochemical outcome is analogous to others described for similar systems,[22a,23] and is most likely the result of a rare example of anchimeric assistance by the azido group[15c,22a,b,24] prior to rearrangement (Scheme 6). Treatment of **33** with one equivalent of PMe_3,[21] followed by aqueous basic workup[25] afforded the α,β-unsaturated aldehyde **34** as the only detectable product.



Scheme 6 Anchimeric assistance by the azido group to afford compound **33**.

Conclusion

We developed synthetic routes that allow for the synthesis of 4′-deoxy-4′-fluoro neamine **22** and 4′-deoxy-4′-fluoro 4′-*epi* neamine **20** from paromamine and neamine as starting materials.

The fluorinated compounds are being studied by NMR to determine the variation of pK_a due to replacement by fluorine of the 4′-OH with retention or inversion of configuration. In the course of these synthetic studies, we encountered interesting by-products resulting from anchimeric assistance and ring contraction. Vinyl azide **30** and the aldehyde **34** are versatile functionalized derivatives of neamine that may find utility in further synthetic efforts. We are currently adapting the methodology developed in this study to the synthesis of 4′-deoxy-4′-fluoro neomycin and its 4′-*epi* variant.

Table 3 Chemical shift assignments for selected compounds. Ring I only[a,e]

	δ/ppm, J/Hz				
	32[b]	**25**[b]	**29**[b]	**22**[c]	**20**[d]
H-1′	5.65	5.67	5.56	5.27	5.38
H-2′	3.75	3.30	3.18	2.84	3.10
H-3′	5.33	4.19	5.60	3.85	3.85
H-4′	4.91	4.85	4.46	4.23	4.84
H-5′	4.33	4.04	4.34	3.97	4.09
H-6a′	3.39	3.35	3.51	2.82	2.91
H-6b′	3.63	3.66	3.64	2.99	2.95
$J_{1',2'}$	3.5	3.7	3.6	3.5	3.9
$J_{2',3'}$	11.3	9.8	10.9	10.5	11.0
$J_{3',4'}$	2.5	8.8	8.9	8.7	2.5
$J_{4',5'}$	—	10.1	9.8	9.8	—
$J_{5',6a'}$	7.7	3.0	4.7	6.8	5.2
$J_{5',6b'}$	5.5	6.9	2.4	3.2	7.9
$J_{6a',6b'}$	12.8	13.5	13.5	13.8	13.5
$J_{1',F}$	—	—	2.8	3.5	—
$J_{2',F}$	—	—	1.0	nd	0.8
$J_{3',F}$	26.6	—	13.8	14.7	30.0
$J_{4',F}$	50.8	—	50.0	51.1	51.1
$J_{5',F}$	29.2	—	4.7	3.2	30.9
$J_{6a',F}$	—	—	1.4	nd	—
$J_{6b',F}$	—	—	1.5	2.2	1.0

[a] J_{H-F} coupling constants measured in proton spectra. [b] 400 MHz, $CDCl_3$. [c] 400 MHz, D_2O, free base. [d] 500 MHz, D_2O, free base. [e] For other protons see experimental procedures and Table S1 in ESI.

Acknowledgements

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