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A Stevens rearrangement thwarts glycosylation with liposidomycin diazepanone ribofuranosyl donors

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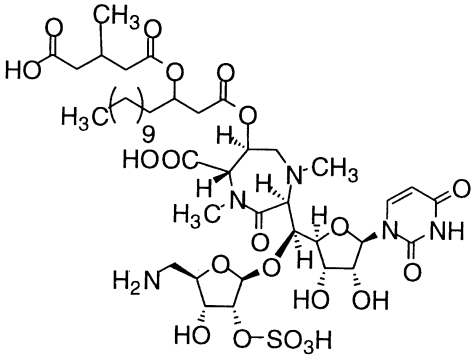
Abstract—Attempted Vorbrüggen and related glycosylations with ribofuranosyl acetates fail in the liposidomycin series when there is a nucleophilic amine six atoms from the anomeric center. Instead, the nitrogen participates, and a stereoselective Stevens rearrangement ensues.

Unless one starts with a commercially available nucleoside, the synthesis of a complex nucleoside antibiotic,[1] such as liposidomycin C (**1**),[2,3] requires *N*-glycosylation at some point in the route. The Vorbrüggen nucleoside synthesis,[4] featuring the reaction of an anomeric acetate with a silylated purine or pyrimidine under the influence of a Lewis acid, is well-suited for a variety of these couplings. Where the Vorbrüggen reaction is unsuccessful or where the anomeric acetate is otherwise unsuitable,[5–7] the NIS-promoted synthesis of the nucleoside from the thioglycoside can be an excellent alternative.[1,8]



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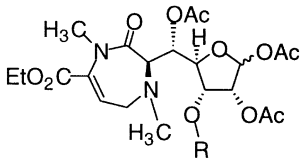
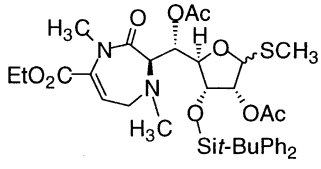
In the course of studies directed at elucidating the stereochemistry on and near the diazepanone ring of **1**,[9] we attempted numerous *N*- and *S*-glycosylations of the donors **2** and **3**. In no case was an appreciable quantity of the desired nucleoside or thioglycoside formed. Instead, mixtures were obtained, which also included much low R_f material by silica TLC. In several *N*- and *S*-glycosylation reactions of **2**, however, the same (or with **3**, analogous) high R_f product was detected by TLC and NMR, and in one case it was isolated in sufficient quantity and purity to permit full spectroscopic characterization. Thus, the combination of the triacetate **2**, (methylthio)trimethylsilane (10 equiv.), and trimethylsilyl trifluoromethanesulfonate (2.5 equiv.) in dry carbon tetrachloride solution was heated at reflux for 3 h, whereupon **2** was consumed. Although a trace of the expected[10] thioglycoside **4** was present, preparative TLC of the reaction mixture gave as the major product a rearranged diacetate **5** (LC-FAB-MS m/z 665, MH+ for $M = C_{38}H_{50}N_2O_9Si$) in 60% yield.



2: R = Si*t*-BuPh$_2$
3: R = COCH$_3$



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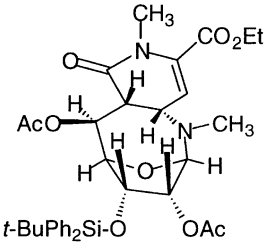

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Table 1. ^{1}H and ^{13}C NMR assignments for **5**

Position	δ (H)	Multiplicity	NOESY crosspeaks	δ (C)	HMBC crosspeaks
2				170.2	H-4,14
3	2.41	dd, $J=5.1$, 6.2	H-4,7,9	47.77	H-4,5,8
4	3.65	t, $J=5.1$	H-3,5,9,10,13	53.17	H-3,5,11,13
5	6.33	d, $J=4.4$	H-4,11,13	121.01	H-3,4
6				133.31	H-4,5,14
7	5.48	t, $J=6.2$	H-3,8	70.25	H-3,4,8,9
8	4.32	dd, $J=3.4$, 5.4	H-7,9	84.93	H-10,11
9	4.93	dd, $J=3.6$, 5.6	H-3,4,8,10	73.12	H-8,11
10	4.55	d, $J=5.5$	H-4,9,11,13,21	76	H-9,11
11	4.23	s	H-5,10,13,21	97.54	H-4,8,9,10,13
13	2.2	s (3H)	H-4,5,10,11	36.76	H-4,11
14	3.01	s (3H)		31.47	
15				162.21	H-4,5,16
16	4.21	app qd, $J=1$, 6.9	H-17	61.79	H-17
17	1.27	t, $J=6.9$ (3H)	H-16	13.26	H-16
18				169.58	H-19
19	1.65	s (3H)		19.85	
20				170.1	H-10,21
21	1.83	s (3H)	H-10,11	20.19	
22				18.95	H-23
23	1.02	s (9H)		26.18	
24				Not observed	
25	7.74	d, $J=7$ (2H)		135.99	H-25,25′,26,27
25′	7.63	d, $J=7$ (2H)		135.76	H-25,25′26,27
26	7.38–7.49	m (4H)		128.04	H-25,25′
27	7.38–7.49	m (2H)		130.31	H-25,25′,26

The structure and stereochemistry of **5** were determined by NMR analysis. The nearly first-order 600-MHz ^{1}H NMR spectrum of **5** in CD_3CN solution (Table 1) indicates the loss of one acetate, but the retention of all other functionality present in **2** including the tertiary amine. COSY and LR-COSY analysis facilitated the assignment of individual signals and established the proton connectivity among the eight contiguous C-H's: H-5, 4, 3, 7, 8, 9, 10, and 11, respectively (arbitrary numbering as shown in Fig. 1). Non-vicinal NOESY crosspeaks (shown on **5** in Fig. 1) indicate the stereochemical β–*syn* relationship of H-3, H-4, H-9, H-10, and NCH_3. The structure drawn for **5** is consistent with the observed vicinal proton coupling constants (e.g. $J_{10,11}\sim 0$ Hz) and with the absolute stereochemistry of the starting material, **2**, at C-7, C-8, C-9, and C-10. The 150-MHz ^{13}C NMR spectrum (Table 1) was fully assigned (except for the Ph *ipso* C-24), and the carbon connectivity confirmed, by using HSQC and HMBC (see Table 1) techniques.

The conversion of **2** to **5** is formally a Stevens rearrangement, which normally occurs under strongly basic conditions.[11] Given the Lewis acidic conditions of this stereoselective rearrangement, however, the intermediacy of a carbanion would not be expected. A mechanism is proposed in Scheme 1. Loss of acetate promoted by TMS-OTf and accompanied by least-motion *N*-participation on the furanose β-face would lead to the anomeric ammonium salt **6**. Elimination assisted by *O*-silylation of the amide would give the iminium intermediate **7**, and then Mannich-like ring closure provides the product **5**. A tetrahydro-oxazine chair conformation for **6** that places the bonds to be broken in good alignment for a *trans–anti* elimination (the diazepanone ring would be in a pseudo-boat; see below) can be easily reached, and this conformation correlates with *E* geometry for the silyl enol ether and *Z* geometry for the iminium. The C-3,4 *cis* ring fusion stereochemistry of **5** would result from a conformation of **7** that allows the *Re* face of the silyl enol ether C-3 to approach the *Re* face of the iminium C-4, as illustrated. According to the NOESY results, the product **5** has undergone a conformational change after the cyclization to bring H-4 and H-9 closer together.

In glycosylation reactions that were not heated, tetraacetate **3** was partly converted to low R_f material that could nevertheless be isolated by preparative TLC on

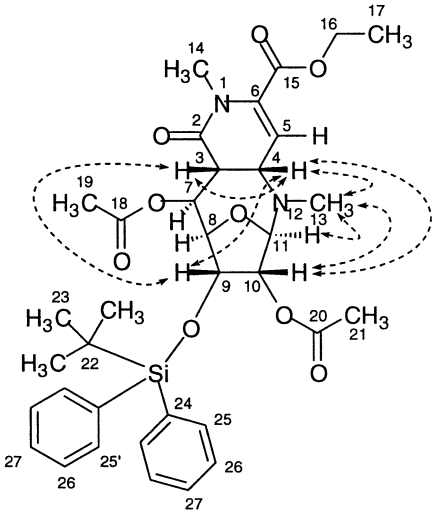
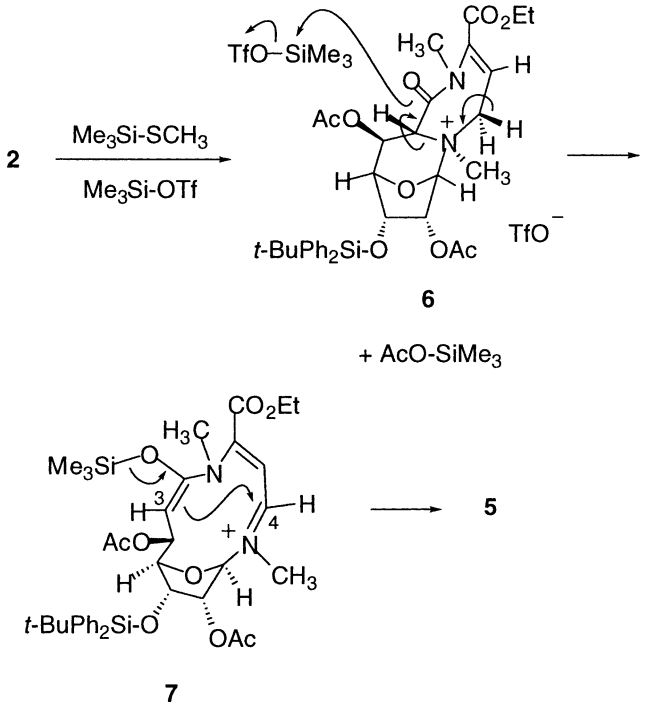


Figure 1. Numbering and selected NOESY crosspeaks for **5**.



Scheme 1. Proposed mechanism for Stevens rearrangement of **2**.

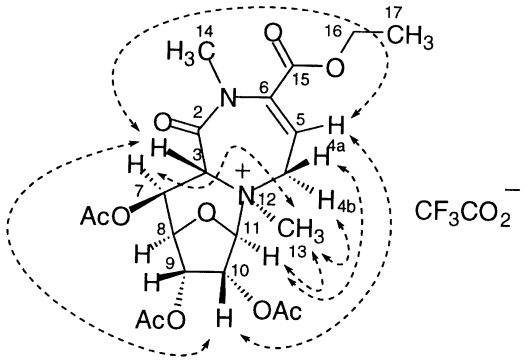


Figure 2. Numbering and selected NOESY crosspeaks for **8**.

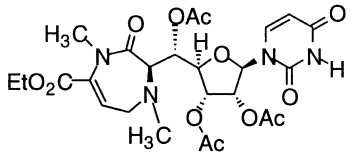
silica with 80:20:1 ethyl acetate/methanol/acetic acid as the eluant, followed by reverse phase HPLC with 9:1 acetonitrile/water containing 0.1% TFA as the eluant (33% yield). MS (m/z 469, $M^+ = C_{21}H_{29}N_2O_{10}$) and ^{1}H NMR analysis indicated this material to be the anomeric ammonium furanoside trifluoroacetate salt **8** (Fig. 2) analogous to the presumed intermediate (**6**) for formation of **5**. Complete structure elucidation for **8**, including stereochemistry, conformation, and ^{1}H and ^{13}C assignments, was obtained by COSY, NOESY, HSQC, and HMBC analysis. In particular, strong HMBC crosspeaks between the $\underline{C}H_3$–N^+ (H-13) and three carbons at δ 102.6, 60.3, and 58.6 (C-11, C-3, and C-4, respectively, Table 2) confirm that the amine is quaternary.[12] Non-vicinal NOESY crosspeaks (shown in Fig. 2) indicate R stereochemistry at the N^+ atom, with the tetrahydro-oxazine ring in a chair conformation that bears axial $^+$N-CH_3 and equatorial -OCOCH_3 substituents, respectively. The 1,4-diazepan-3-one ring of **8** is in a pseudo-boat conformation ('^{3}B^{6,7}') as depicted for **6**, consistent with a four bond 'W' coupling between N–$\underline{C}$=O and the anomeric proton H-11 in the HMBC spectrum.

The problem of N-participation with liposidomycin diazepanone ribofuranosyl donors during the Vorbrüggen reaction was finally solved by preforming the hydrochloride salt of the donor **3**.[9] Even with the tertiary amine initially protonated, the reaction of **3** with bis(trimethylsilyl)uracil gave much low R_f material. However, the required uracil nucleoside **9** was isolated in 18% yield, which was sufficient for the constitutional synthesis.[9] Development of a method for more effective N-protection during glycosylation, one

Table 2. ^{1}H and ^{13}C NMR assignments for **8**

Position	δ (H)	Multiplicity	NOESY crosspeaks	δ (C)	HMBC crosspeaks
2				160.3	H-3,7,11 (4-bond 'W'),14
3	4.42	d, J=10.7	H-5,9,10	60.3	H-4a,7,8,11,7-Ac
4a	4.43	dd, J=15, 8.2	H-4b,5,11	58.6	H-3,5,11,13
4b	4.26	dd, J=15, 5.9	H-4a,13	–	–
5	6.88	dd, J=8.2, 5.9	H-3,4a,10	121.2	H-4ab,13
6				142.4	H-4ab,5,14
7	5.63	dd, J=10.7, 4.5	H-8,13	60.5	H-3,9,7-Ac
8	4.89	d, J=4.5	H-7,9	82.3	H-3,7,9,10,11
9	5.65	d, J=6.7	H-3,8,10	70.6	H-7,8,10,11, 9-Ac
10	5.48	d, J=6.6	H-3,5,9,11	71.3	H-8,9,11,10-Ac
11	5.37	s	H-4a,10,13	102.6	H-3,4ab,8,9,10,13
13	3.29	S (3H)	H-4b,7,11	49.3	H-3,4ab,11
14	3.16	S (3H)		34.4	Not determined
15				161.1	H-5,16
16	4.31	app ddq, J=17, 12, 7 (2H)	H-17	62.9	H-17
17	1.33	t, J=7 (3H)	H-16	13.2	H-16
7-Ac	1.99	s (3H)		19.8, 168.7	H-7,7-Ac
9-Ac	2.06	s (3H)		19.6, 170.0	H-9,9-Ac
10-Ac	2.13	s (3H)		19.6, 170.3	H-10,10-Ac

that might foster the total synthesis of **1**, is the subject of ongoing studies.



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Acknowledgements

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References

1. Knapp, S. *Chem. Rev*. **1995**, *95*, 1859–1876.
2. Isono, K.; Uramoto, M.; Kimura, K.; Izaki, K.; Nelson, C. C.; McCloskey, J. A. *J. Antibiot*. **1985**, *38*, 1617–1621.
3. Knapp, S.; Morriello, G. J.; Nandan, S. R.; Emge, T. J.; Doss, G. A.; Mosley, R. T.; Chen, L. *J. Org. Chem*. **2001**, *66*, 5822–5831 and references therein.
4. Vorbrüggen, H.; Ruh-Polenz, C. *Org. React*. **2000**, *55*, 1–630.
5. Knapp, S.; Nandan, S. R. *J. Org. Chem*. **1994**, *59*, 281–283.
6. Knapp, S.; Gore, V. K. *Org. Lett*. **2000**, *2*, 1391–1393.
7. Garner, P.; Yoo, J. U.; Sarabu, R. *Tetrahedron* **1992**, *48*, 4259–4270.
8. Knapp, S.; Shieh, W.-C. *Tetrahedron Lett*. **1991**, *32*, 3627–3630.
9. Knapp, S.; Morriello, G. J.; Doss, G. A. *Org. Lett*. **2002**, *4*, 603–606.
10. Pozsgay, V.; Jennings, H. J. *Tetrahedron Lett*. **1987**, *28*, 1375–1376.
11. Pine, S. H. *Org. React*. **1970**, *18*, 403–464.
12. A simple glycosyl trialkylammonium salt has been recently characterized by X-ray crystallography. See: Skorupowa, E.; Kurszewska, M.; Konitz, A.; Wojnowski, W.; Wisniewski, A. *Carbohydr. Res*. **2001**, *331*, 343–346.