Total Synthesis

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A Modular Approach to the Total Synthesis of Tunicamycins**

*Jiakun Li and Biao Yu**

Abstract: *The tunicamycins constitute a delicate mimic of the bisubstrate intermediates of N-acetyl-D-hexosamine-1-phosphate translocases and thus inhibit bacterial cell-wall synthesis and the N glycosylation of eukaryotic proteins. An efficient approach to the synthesis of this unique type of nucleoside antibiotics is now reported and features the assembly of five modules in a highly stereoselective and robust manner. A Mukaiyama aldol reaction, intramolecular acetal formation, gold(I)-catalyzed O and N glycosylation, and final N acylation were used as the key steps.*

The tunicamycins, which were originally isolated from *Streptomyces lysosuperficus* and *S. chartreusis* in 1971, consist of five structural units, namely uracil, ribose, galactosamine (GalN), *N*-acetylglucosamine (GlcNAc), and a fatty acid (Figure 1).[1] Unique are the tail-to-tail C–C linkage between the ribose and GalN units (C5′–C6′), which leads to the formation of an undecose (namely tunicamine), and the head-to-head glycosidic linkage between the GalN and GlcNAc units (C11′–O–C1″). Similar antibiotics that were recently isolated from other sources include the streptovirudins and corynetoxins,[2,3] which show structural variations only at the acyl moiety and the uracil unit (with 5,6-dihydrouracil as an alternative).[1–4] Structurally, these acyl nucleoside antibiotics constitute a delicate mimic of the bisubstrate intermediates of bacterial translocase I and the eukaryotic GlcNAc-1-P transferase,[5] which synthesize precursors crucial to bacterial cell-wall synthesis and the N glycosylation of eukaryotic proteins. Therefore, tunicamycins show potent inhibitory effects against microbes as well as mammalian cells.[4] Owing to their capability of inhibiting protein N glycosylation, the use of tunicamycins has become a routine method for studying the functions of asparagine-linked glycans (N-glycans).[6] However, tunicamycins have always been used as a complex mixture, and congeners with minor variations at the acyl moiety might have different activities.[7] Furthermore, the tunicamycins might also inhibit other glycosyltransferases or even other enzymes that recognize the uridine motif.[5] To conduct structure–activity relationship (SAR) studies and to develop a specific inhibitor (especially of clinical usefulness), a synthetic method that provides access to pure samples of a single tunicamycin and modified analogues is required.[8]

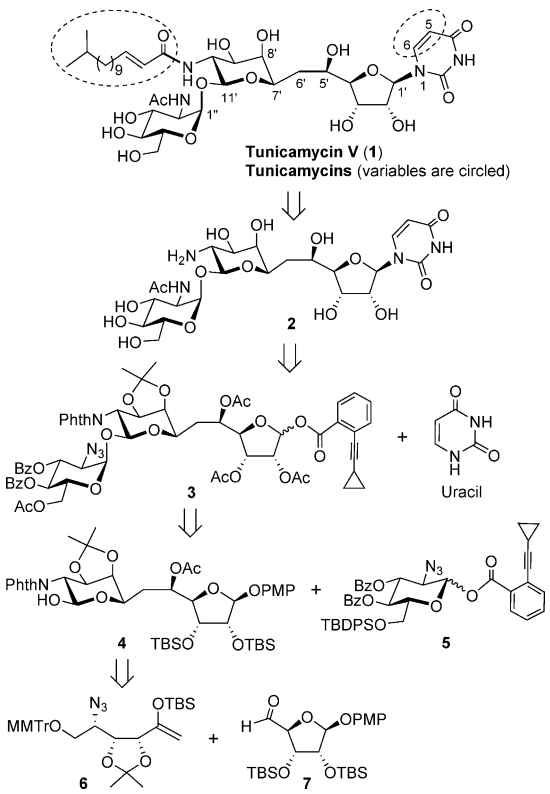

Figure 1. Tunicamycins and a retrosynthetic analysis. Ac = acetyl, Bz = benzoyl, Phth = phthaloyl, PMP = *para*-methoxyphenyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Indeed, tremendous efforts have been devoted towards the chemical synthesis of tunicamycins;[9–15] however, only two successful total syntheses have been described.[9,10] Suami et al. applied a Henry condensation to form the C5′–C6′ bond and a Koenigs–Knorr-type glycosylation to construct the C11′–O–C1″ linkage, but both the elaboration of the 5′-hydroxy group from the nitroaldol adduct and the formation of the β,α-11′,1″-trehalose were non-stereoselective and low-yielding.[9b,c] Myers et al. achieved an elegant total synthesis by employing a Schmidt glycosylation with a GalNPhth lactol as the acceptor and a $GlcN_3$ imidate as the donor to build the β,α-trehalose linkage at an early stage of the synthesis. An intramolecular reductive coupling of an *exo*-glycal with a uridine acetal unit tethered via an *O*-dimethylsilyl hemiselenoacetal (between C8′ and C5′) was employed to build the C5′–C6′ bond with high stereoselectivity.[10b,c] Both syntheses installed the acyl moiety in the final step (from **2**), so that access to all of the tunicamycin congeners should be feasible.[16]

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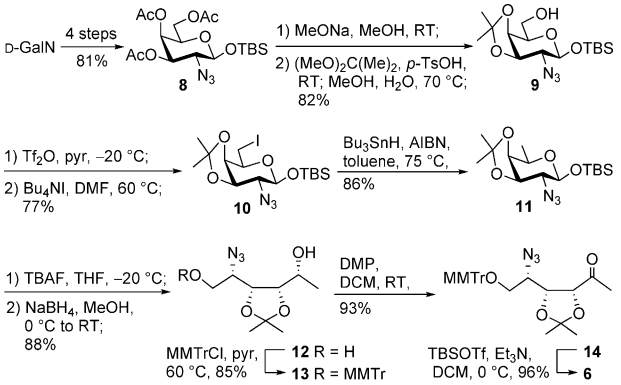
We attempted to condense the GalN and ribose units in a stereoselective and intermolecular manner, encouraged by a recent finding on the biosynthesis of the tunicamycin C5′–C6′ bond.[8a] Linear silyl enol ether **6** and aldehyde **7** were thus successfully coupled through a Mukaiyama aldol reaction (Figure 1). Furthermore, we envisioned that a fully modular assembly could be possible by utilizing the recently developed gold(I)-catalyzed glycosylation (with donors **5** and **3**) for the trehalose synthesis and a late-stage N glycosylation to install the nucleobase unit.[17–19]

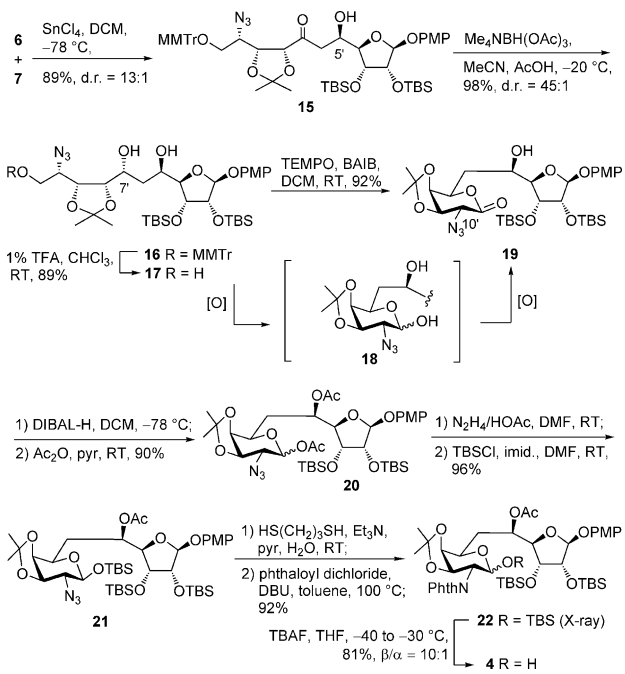
Silyl enol ether **6** was derived from D-GalN (Scheme 1). Therefore, 2-azido-1-*O*-TBS derivative **8** was prepared from



Scheme 1. Synthesis of silyl enol ether **6**. AIBN = 2,2′-azobis(isobutyronitrile), DCM = dichloromethane, DMP = Dess–Martin periodinane, MMTr = monomethoxytrityl, *p*-TsOH = *para*-toluenesulfonic acid, pyr = pyridine, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl.

D-GalN following a literature approach;[20] removal of the acetyl groups followed by selective protection of the resultant 3,4-hydroxy groups as their isopropylidene acetal gave **9** (82%).[21] The 6-hydroxy group in **9** was removed by triflate formation, substitution with iodide, and radical reduction, providing 6-deoxypyranoside **11** (66% over 3 steps). The conditions of the radical reduction (Bu_3SnH, AIBN, toluene, 75 °C, 1 h) did not considerably affect the 2-azido group. The anomeric TBS group was then cleaved with TBAF, and the resulting lactol was reduced into linear diol **12** with $NaBH_4$ (88% over 2 steps).[22] The primary hydroxy group in **12** was protected as its MMTr ether (85%), and the secondary hydroxy group was then oxidized into the corresponding ketone with DMP (93%). The resultant methyl ketone **14** was converted into the desired silyl enol ether **6** (96%), which could be easily purified and was found to be shelf-stable.

A chelation-controlled Mukaiyama aldol reaction of **6** and aldehyde **7**[23] would provide the desired β-hydroxyketone **15** in a stereoselective fashion (Scheme 2).[24] Commonly used Lewis acid promoters (i.e., $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$, $TiCl_4$, and $SnCl_4$) were examined for the present condensation (Supporting Information, Figure S1); the best results were attained with $SnCl_4$ (CH_2Cl_2, −78 °C), leading to adduct **15** in 89% yield and 13:1 diastereoselectivity. A subsequent Evans–Saksena 1,3-*anti* reduction provided diol **16** in excellent yield and diastereoselectivity (98%, d.r. = 45:1).[15,25] The

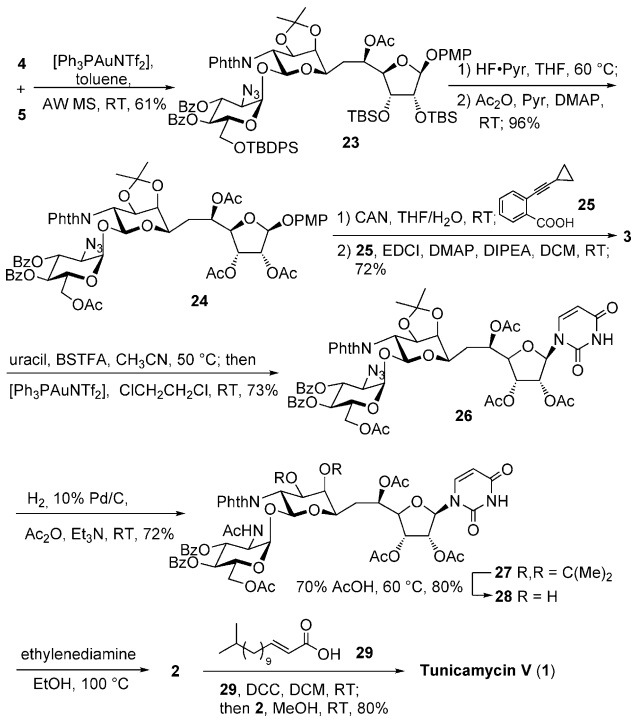


Scheme 2. Synthesis of undecose derivative **4**. BAIB = bis(acetoxy)iodobenzene, DIBAL-H = diisobutylaluminum hydride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl, TFA = trifluoroacetic acid.

MMTr ether was cleaved to provide triol **17** (89%). Selective oxidation of the primary hydroxy group in **17** was achieved in the presence of TEMPO and BAIB;[26] simultaneous acetal formation led to pyranose **18**, which, however, immediately oxidized to lactone **19** (92%). Azidolactone **19** readily underwent epimerization ($CDCl_3$, RT) at the C10′ position (Figure S2),[27] and was thus quickly reduced into lactol **18** with DIBAL-H. Subsequent acylation led to tunicamine derivative **20** (90% over 2 steps). Transformation of the azido group in **20** into an *N*-Phth moiety was found to be troublesome owing to the migration of the neighboring *O*-acetyl group onto the nascent amino group under a variety of conditions tested for the reduction of the azide (Ph_3P, Zn/HOAc, or PhSeH/Et_3N). Therefore, the anomeric acetyl group was replaced with a TBS group (96% over 2 steps). Treatment of the resultant compound **21** with 1,3-propanedithiol led to the corresponding amine,[28] which was protected with a phthaloyl group to afford **22** (92% over 2 steps). Crystalline **22** could be analyzed by X-ray diffraction[34] (Figure S3) to confirm the stereochemistry (at C5′ and C7′) proposed in the previous syntheses. Selective cleavage of the anomeric TBS ether in **22** was achieved with TBAF to afford hemiacetal **4** (81%),[29] with the desired β anomer occurring predominantly ($\beta/\alpha \approx 10{:}1$).[10b,c,12a,d,e]

The required GlcN *ortho*-alkynylbenzoate **5** was prepared from D-GlcN (68% over 9 steps, see the Supporting Information). The installation of the non-participating azide at the C2 position and a bulky TBDPS group at the 6-hydroxy moiety were expected to facilitate the α-selective glycosylation.[30] After briefly screening the reaction conditions for the glycosylation of lactol **4** and donor **5** (Figure S4), we were

able to obtain the desired β,α-trehalose **23** in a satisfactory yield of 61% ([$Ph_3PAuNTf_2$] (0.4 equiv), toluene, RT; Scheme 3), with the β,β-, α,α-, and α,β-trehaloses being isolated in approximately 4–13% yield (compounds S16–S18).



Scheme 3. Completion of the synthesis of tunicamycin V (**1**). AW MS = acid-washed molecular sieves, BSTFA = *N,O*-bis(trimethylsilyl)trifluoroacetamide, CAN = ceric ammonium nitrate, DCC = 1,3-dicyclohexylcarbodiimide, DIPEA = *N,N*-diisopropylethylamine, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

To facilitate the later N glycosylation, the silyl groups in **23** were replaced with acetyl groups (96% over 2 steps). The resulting compound **24** was subjected to selective removal of the anomeric *para*-methoxyphenyl group with CAN[31] and ester formation with **25** to provide the desired trisaccharide donor **3** (72% over 2 steps). Even with a donor as complicated as **3**, the N glycosylation of uracil still proceeded smoothly to afford the desired nucleoside **26** in a satisfactory 73% yield by silylating uracil with BSTFA in CH_3CN and subjecting the resulting intermediate to the coupling with **3** in the presence of [$Ph_3PAuNTf_2$] (0.2 equiv) in $ClCH_2CH_2Cl$.[18]

The final stage of the synthesis required four straightforward steps. 1) The azide in **26** was directly converted into the acetamide (H_2, 10% Pd/C, Ac_2O, Et_3N, RT), which gave **27** (72%).[32] 2) The isopropylidene acetal was cleaved (70% HOAc, 60 °C) to give diol **28** (80%). 3) The *N*-Phth group together with the benzoyl and acetyl groups were cleanly removed with ethylenediamine in ethanol at reflux,[33] affording the key precursor **2**. 4) Finally, selective N acylation of **2** (or with preceding hydrogenation of the uracil moiety)[16] would lead to any one of the tunicamycin congeners.[9c,10c] We chose to synthesize tunicamycin V (**1**), the most abundant congener, as an example. Therefore, fatty acid **29** (6.0 equiv) was activated by stirring with DCC (9.0 equiv) in CH_2Cl_2 at RT for 30 minutes; aliquots of the solution (1.0 equiv each) were then added to a solution of **2** in MeOH at eight-hour intervals over two days, furnishing tunicamycin V (**1**) in 80% yield.

In conclusion, an efficient approach to the total synthesis of tunicamycins has been developed, and the assembly of the five readily accessible and stable modules into the final antibiotic required only 21 steps, which proceeded with an overall yield of approximately 6%. The challenging glycosyl tail-to-tail (C5′−C6′) and head-to-head (C1″−O−C11′) linkages were constructed by a Mukaiyama aldol reaction (**6** and **7**) and a gold(I)-catalyzed glycosylation (**4** and **5**), respectively; both processes occurred with high stereoselectivity. With the gold(I)-catalyzed glycosylation, a later-stage nucleoside synthesis was also achieved (**3** and uracil), which provides an opportunity to prepare neo-tunicamycins with different nucleobases. In fact, various tunicamycin analogues could be accessed by varying any of the modules in the present synthesis, which should facilitate SAR studies on this important type of glycosyltransferase inhibitors.

Keywords: glycosylation · gold · nucleosides · total synthesis · tunicamycin

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[34] CCDC 1045556 (**22**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Communications

Total Synthesis

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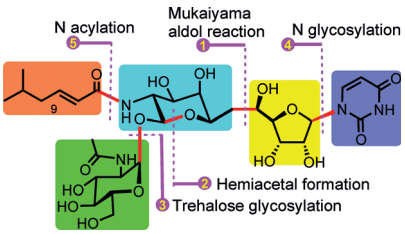
A Modular Approach to the Total Synthesis of Tunicamycins



The modular and stereoselective synthesis of tunicamycins features a Mukaiyama aldol reaction, intramolecular acetal formation, gold(I)-catalyzed O and N glycosylation, and final N acylation as the key steps. These natural products are a unique type of nucleoside antibiotics with potent inhibitory activities against bacterial cell-wall synthesis and the N-glycosylation of eukaryotic proteins.