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Total Synthesis of Vineomycin B_2

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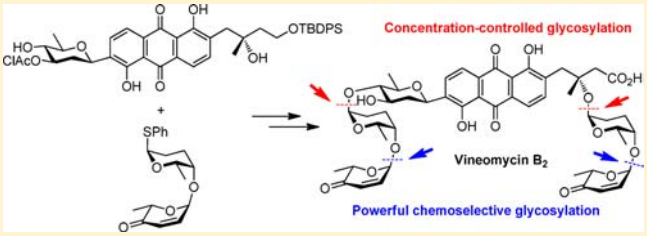
Supporting Information

ABSTRACT: The first total synthesis of vineomycin B_2 (**1**) has been accomplished. The aglycon segment, a vineomycinone B_2 derivative, and the glycon segment, an α-L-acurosyl-L-rhodinose derivative, were prepared via C-glycosylation using an unprotected sugar and powerful chemoselective O-glycosylation using a 2,3-unsaturated sugar, respectively, as the key steps. Furthermore, effective and simultaneous introduction of the two glycon moieties to the aglycon part by concentration-controlled glycosylation led to the total synthesis of **1**.



1. INTRODUCTION

Vineomycin B_2 (**1**), an anthracycline antibiotic, was isolated by Ōmura et al. from the culture broth of *Streptomyces matensis* subsp. *vineus*.[1] **1** is active against Gram-positive bacteria and sarcoma 180 solid tumors in mice.[1a] The key structural features of **1** are an aryl *C*-glycoside scaffold with a side chain containing a β-oxo-*tert*-alcohol subunit in the aglycon and two identical deoxydisaccharides, α-L-acurosyl-α-L-rhodinoses, in the glycon.[1b] Because of its important biological activity and novel molecular architecture, **1** is a prime target for chemical synthesis. Indeed, six elegant syntheses of the aglycon, vineomycinone B_2 methyl ester (**2**), have been reported so far.[2] In addition, synthetic studies of the deoxyoligosaccharide portion of the vineomycin family and related antibiotics have also been reported.[3] However, the total synthesis of **1** with its two deoxydisaccharides has not been accomplished to date (Figure 1). One of the major tasks in the synthesis of **1** is the introduction of the highly deoxygenated and acid-labile deoxydisaccharide (α-L-acurosyl-α-L-rhodinose) to the β-oxo-*tert*-alcohol in the aglycon. It is well-known that β-oxo-*tert*-alcohols are difficult to glycosylate because of both the intramolecular hydrogen bonding between the hydroxy group and the carbonyl oxygen and the ease of β-elimination of the *tert*-hydroxy group β to the carbonyl group.[4] Indeed, model studies in our laboratories have shown that even without the β-oxo moiety, homobenzylic tertiary alcohols are challenging to use as glycosyl acceptors, showing a propensity to undergo dehydration under standard Lewis acid-mediated glycosylation conditions.[5] Therefore, any synthesis of **1** is going to require a careful strategy to tune the glycosyl donor and acceptor's inherent reactivity to allow the desired bond formation without dehydration. Herein, we report the first total synthesis of **1**, utilizing our powerful chemoselective O-glycosylation methodology employing 2,3-unsaturated and 2,3-saturated deoxysugars.[6] To the best of our knowledge, this is the first example of a total synthesis of a natural product that possesses an oligosaccharide attached to a *tert*-alcohol.[7]

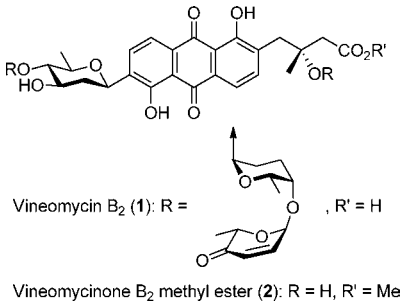


Figure 1. Chemical structures of vineomycin B_2 (**1**) and vineomycinone B_2 methyl ester (**2**).

2. RESULTS AND DISCUSSION

As illustrated in our retrosynthetic analysis (Figure 2), we planned to simultaneously introduce two deoxydisaccharide (α-L-acurosyl-α-L-rhodinose) moieties **4** to the suitably protected aglycon derivative **3** by glycosylation under mild conditions. Furthermore, we expected that the temporary silyl ether at the side chain in **3**, which could be converted to the carboxy function originally found in **1**, would enhance the nucleophilicity of the *tert*-alcohol on the side chain and prevent β-elimination in the glycosylation of **3** and **4**. The aglycon derivative **3** could be prepared in a few short steps by a modified version of Suzuki's synthesis of vineomycinone B_2 methyl ester (**2**)[2d] involving C-glycosylation using unprotected

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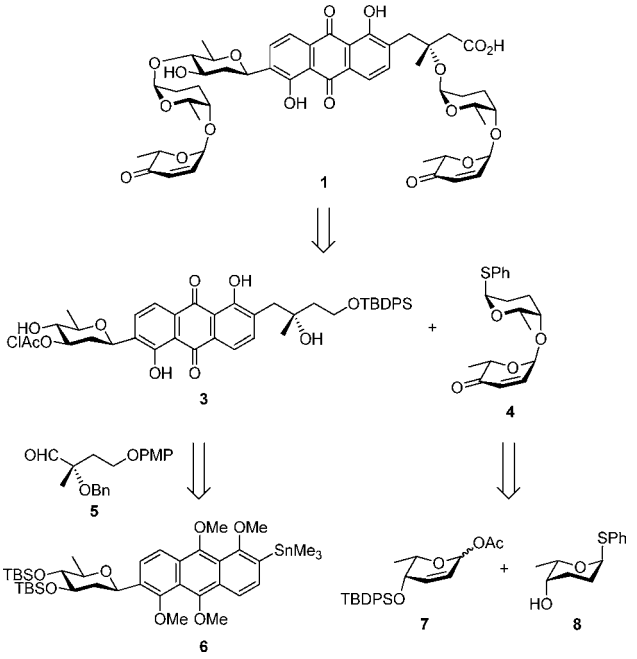


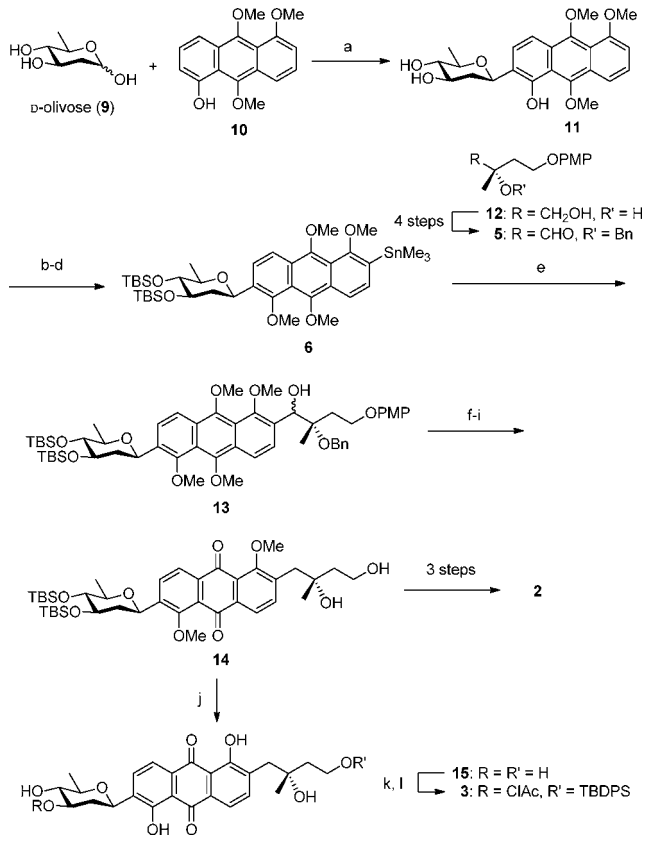
Figure 2. Retrosynthetic analysis of vineomycin B_2 (**1**).

D-olivose[8] and 1,2-addition of the chiral aldehyde **5** and the aryl *C*-glycoside **6**. The glycon derivative **4** would be synthesized utilizing a powerful chemoselective glycosylation methodology[6] with 2,3-unsaturated deoxysugar **7** and 2,3-saturated deoxysugar **8**.

The synthesis of the aglycon derivative **3** is summarized in Scheme 1. First, aryl *C*-glycoside **11** was synthesized by stereo- and regioselective C-glycosylation using unprotected sugar, D-olivose (**9**), and 5,9,10-trimethoxyanthracen-1-ol (**10**) in the presence of TMSOTf.[2d,8,9] Meanwhile, optically pure aldehyde **5** was synthesized from **12** in four steps ((1) tetrahydropyranylation; (2) benzylation; (3) detetrahydropyranylation; (4) oxidation; see Supporting Information). Compound **12** was prepared from 3-methyl-3-buten-1-ol in 2 steps according to Martin's procedure.[2e] The aryl *C*-glycoside **11** was converted to arylstannane **6** (Suzuki's intermediate)[2d] in three steps ((1) methylation; (2) silylation; (3) stannylation), which was then lithiated and treated with aldehyde **5** to afford **13**. Subsequent benzoylation of the benzylic alcohol in **13** and treatment of the resulting benzoate with CAN gave the corresponding anthraquinone derivative, whose benzyl ether was removed by hydrogenolysis, followed by deoxygenation at the benzylic position using $Na_2S_2O_4$ to provide diol **14**. Deprotection of all the silyl and methyl groups of **14** with BBr_3 gave hexaol **15**. At this stage, the structure of **15** including the optical purity was confirmed by the conversion of diol **14** to vineomycinone B_2 methyl ester (**2**) in three steps ((1) oxidation; (2) deprotection; (3) methyl esterification; see Supporting Information). Finally, selective protection of the primary alcohol in **15** with a TBDPS group, followed by selective protection of the C3 secondary alcohol in the D-olivose moiety with a chloroacetyl (ClAc) group, furnished the suitably protected aglycon derivative **3**.

The synthesis of glycon donor **4** was achieved as illustrated in Scheme 2. Acurosyl segment **7** possessing the 2,3-unsaturated glycosyl acetate as a superarmed sugar[6] was prepared from known *p*-methoxyphenyl (PMP) glycoside **16**.[10,11] Thus, silylation of the C4 secondary alcohol of **16** with a TBDPS

Scheme 1. Synthesis of Aglyconderivative 3 and Vineomycinone B_2 Methyl Ester (2)[a]



[a]Reagents and conditions: (a) TMSOTf, MeCN, rt, 45% (recovered **6**, 29%); (b) K_2CO_3, MeI, acetone, reflux, 95%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 85%; (d) *n*-BuLi, *t*-BuOK, THF, −94 °C; then Me_3SnCl, −94 °C, 74%; (e) MeLi, toluene, −78 to 30 °C; then **5**, 30 °C, 86% (dr 51:49); (f) BzCl, DMAP, pyridine, rt, 83%; (g) CAN, $MeCN/H_2O$ (10/1, v/v), rt, 89%; (h) 10% Pd/C, H_2, EtOH, rt, 98%; (i) $Na_2S_2O_4$, 1 N NaOH, dioxane/H_2O (4/1, v/v), rt, 89%; (j) BBr_3, CH_2Cl_2, −78 °C, 94%; (k) TBDPSCl, imidazole, CH_2Cl_2, rt, 99%; (l) Bu_2SnO, MeOH, reflux; then ClAcCl, pyridine, CH_2Cl_2, 0 °C, 50%.

group followed by deprotection of the PMP group and acetylation at the C1 position gave the superarmed sugar **7**. Hydrogenation of the olefin in **7** using Rh/Al_2O_3 in a mixture of EtOAc and toluene afforded 2,3-saturated sugar **17**.[12] Rhodinose segment **8** possessing the 2,3-saturated thioglycoside structure as an armed sugar[6] was obtained from glycosyl acetate **17**.[11] Thus, conversion of the acetyl group in **17** to a thiophenyl group using PhSH and TMSOTf afforded thioglycoside **18**, whose TBDPS group was then removed using TBAF to give **8**. Chemoselective glycosylation of **8** (an armed sugar) with **7** (a superarmed sugar) using TBSOTf as an activator effectively proceeded at −98 °C under very mild conditions to give the disaccharide **19** possessing a phenylthio group at the C1 position in high yield with high α-stereoselectivity. On the other hand, it was found that TBSOTf-mediated glycosylation of **8** and 2,3-unsaturated 4-ketoglycosyl acetate **20** (a disarmed sugar)[6] did not proceed at −98 °C, while glycosylation at a higher reaction temperature, such as at −78 °C, produced considerable amounts of byproduct **21** arising from the migration of the phenylthio group of **8**. In addition, it was confirmed that glycosylation of **8** and 2,3-saturated glycosyl acetate **17** also did not proceed at −98 °C. These results clearly

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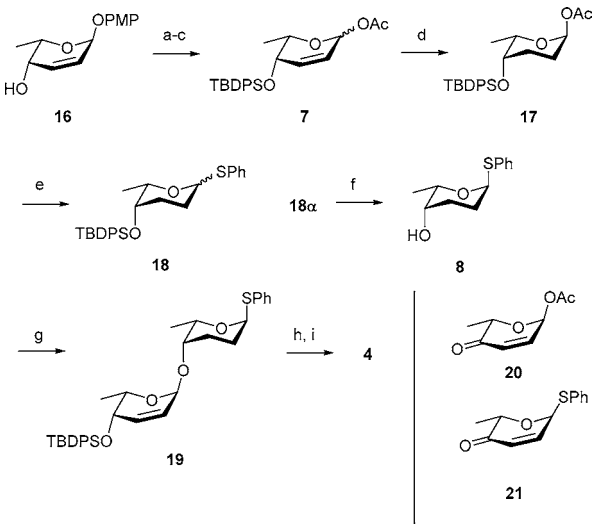
Scheme 2. Synthesis of Disaccharide Donor 4[a]



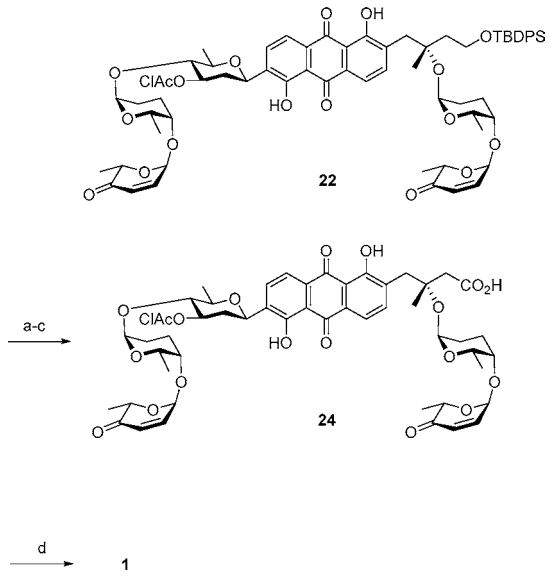
[a]Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 98%; (b) CAN, $NaHCO_3$, MeCN/H_2O (9/1, v/v), 0 °C; (c) Ac_2O, DMAP, pyridine, 0 °C, 91% (two steps, α/β = 87:13); (d) 5% Rh/Al_2O_3, H_2, EtOAc/toluene (9/1, v/v), 0 °C, 87% (α only); (e) PhSH, TMSOTf, CH_2Cl_2, −40 °C, 99% (α/β = 64:36); (f) TBAF, THF, 40 °C, 95%; (g) **7**, TBSOTf, MS 5A, Et_2O, −98 °C, 74% (α only); (h) TBAF, THF, 40 °C, 98%; (i) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 76%.

demonstrate the usefulness of the 2,3-unsaturated sugar as a superarmed glycosyl donor.[6] Finally, deprotection of the TBDPS group in **19** and oxidation of the resulting allyl alcohol afforded thiodisaccharide **4** as a source of the glycon moiety of **1**.

With both the aglycon segment **3** and the glycon segment **4** in hand, we next examined the glycosylation reaction. After many experiments including model studies,[5] we found that the use of NIS/TfOH as activator was effective compared with other activators such as MeOTf, AgOTf, and NBS/TfOH. Thus, glycosylations of acceptor **3** and donor **4** using NIS/TfOH were carried out under several conditions. These results are summarized in Table 1. When 3.0 equiv of **4** was used under low concentration conditions (10 mM for **3**), diglycoside **22** was not obtained, and only monoglycoside **23** was produced in moderate yield. In contrast, when 3.0 equiv of **4** was used under high concentration conditions (25 mM for **3**), the glycosylation effectively proceeded to afford the diglycoside **22** in high yield with α-stereoselectivity. On the other hand, when 1.5 equiv of **4** was used under high concentration conditions (50 mM for **3**), monoglycoside **23** was obtained in high yield with α-stereoselectivity. These results clearly indicate that control of the concentration for the reaction substrates is very important to obtain the desired glycoside in high yield.[13] In all cases, cleavage of the glycosidic bond of the acurosyl moiety was not observed because of the disarmed nature of the acuroside possessing the 2,3-unsaturated-4-keto structure.[6]

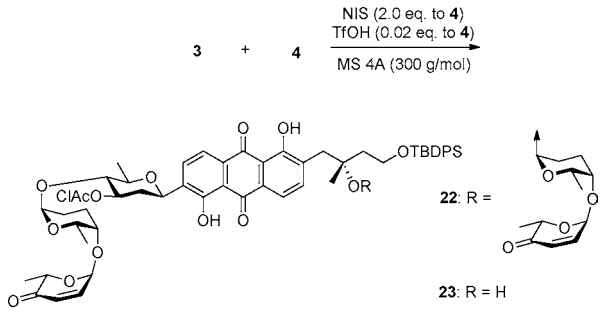
Completion of the synthesis of **1** is summarized in Scheme 3. Deprotection of the TBDPS group in **22** using TASF, followed by oxidation of the resulting primary alcohol, gave carboxylic acid **24**. Finally, deprotection of the ClAc group in **24** with

Scheme 3. Completion of Total Synthesis of 1[a]



[a]Reagents and conditions: (a) TASF, DMF, rt, 80%; (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/THF/H_2O (4/4/3, v/v/v), rt, 93% (two steps); (d) thiourea, 2,6-lutidine, DMF, 60 °C, 91%.

Table 1. Glycosylations Using 3 and 4



entry	amount of **3**, equiv	amount of **4**, equiv	conditions	yield, %		
				22	**23**	**3**
1	1.0	3.0	CH_2CI_2 (10 mM for **3**), −78 to −40 °C, 24 h	trace	31	43
2	1.0	3.0	CH_2CI_2 (25 mM for **3**), −78 to −40 °C, 16 h	88	8	0
3	1.0	1.5	CH_2CI_2 (50 mM for **3**), −78 to −40 °C, 12 h	25	62	trace

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thiourea[14] gave vineomycin B_2 (**1**). Synthetic vineomycin B_2 (**1**) was found to be identical in all respects with the natural product (see Supporting Information).

3. CONCLUSION

In summary, the first total synthesis of vineomycin B_2 (**1**) was achieved. Our synthesis highlights an efficient concentration-controlled glycosylation strategy for introducing acid-labile deoxydisaccharide moieties to the aglycon part. Furthermore, the acid-labile deoxydisaccharide was effectively synthesized by a powerful chemoselective glycosylation methodology using 2,3-unsaturated and 2,3-saturated glycosyl donors. Synthetic studies of other vineomycin family antibiotics are now in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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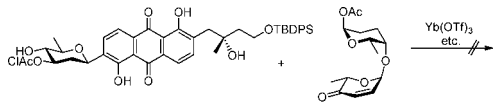
(5) Glycosylations of **3** and **4′**[11] using several activators unfortunately failed because of the predominant dehydration of the *tert*-hydroxy group in **3**.



3 **4′**

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