Concise Total Synthesis of Vicenistatin

Hayato Fukuda,[a] Shiina Nakamura,[a] Tadashi Eguchi,[b] Yoshiharu Iwabuchi,[a] Naoki Kanoh*[a]

[a] Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan
Fax +81(22)7956847; E-mail: kanoh@mail.pharm.tohoku.ac.jp

[b] Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan

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Abstract: A highly convergent total synthesis of macrocyclic lactam glycoside vicenistatin is described. Key features of the synthesis include rapid assembly of the macrolactam part and macrocyclic ring closure via intramolecular Stille coupling.

Key words: vicenistatin, macrolactam, vicenisamine, total synthesis

In 1993, Shindo et al. discovered a novel macrocyclic lactam glycoside, designated as vicenistatin (**1**), from *Streptomyces halstedii* HC-34.[1] Structurally, vicenistatin (**1**) consists of a 20-membered macrolactam and a unique amino sugar vicenisamine (Figure 1). Its relative and absolute stereochemistries were elucidated by NMR analyses[1] and degradation studies,[2] and finally confirmed by the total synthesis.[3] Vicenistatin (**1**) is reported to exhibit in vitro cytotoxicity against human leukemia HL-60 (IC_{50} 0.24 μM) and human colon carcinoma COLO205 (IC_{50} 0.38 μM), and to be effective in a mouse xenograft model.[1] In contrast, its natural congener, vicenistatin M (**2**),[4] which possesses D-mycarose instead of vicenisamine, shows essentially no growth-inhibitory activity against human and mouse cancer cell lines (Figure 1). Vicenisamine is therefore thought to play an important role in the antitumor activity of vicenistatin (**1**). Vicenistatin (**1**) was recently re-discovered as a hit substance from the National Cancer Institute (NCI) libraries using a high-throughput yeast toxicity screen.[5]

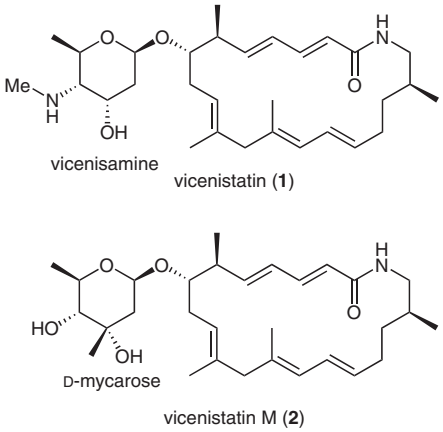

Figure 1 Structure of vicenistains

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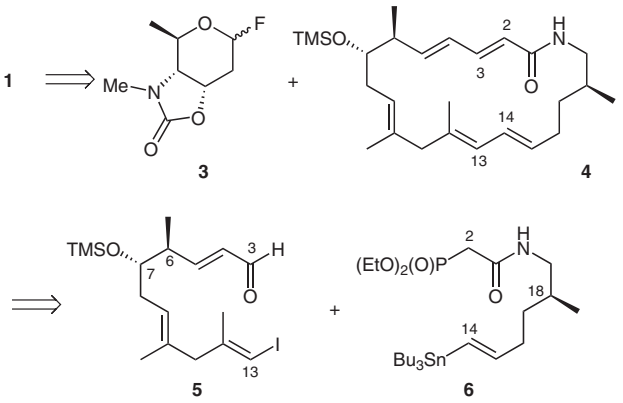
We were intrigued with vicenistatin (**1**) as a potential new cancer therapeutic lead and with its unknown mode-of-action. We report herein a concise total synthesis of vicenistatin (**1**) utilizing a highly convergent strategy.

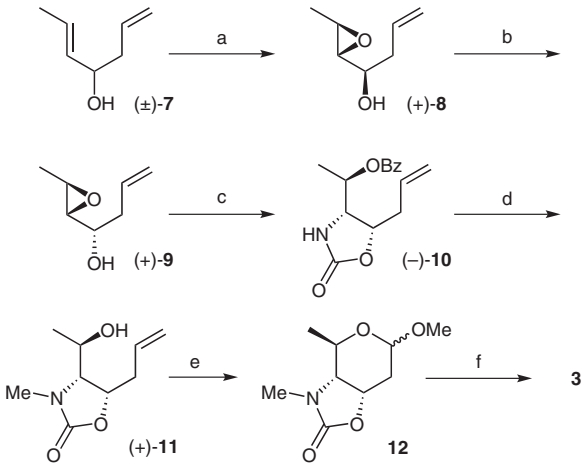
Our retrosynthetic analysis is shown in Scheme 1. Our strategy to vicenistatin (**1**) involves coupling of glycosyl fluoride **3** and macrolactam **4**. To facilitate future structure–activity relationship (SAR) study, we adopted a convergent synthetic strategy by dividing macrolactam **4** into iodoaldehyde **5** and phosphonate **6**. Thus, macrolactam **4** could be obtained through successive coupling reactions; that is, the Horner–Wadsworth–Emmons (HWE) reaction between fragments **5** and **6** followed by intramolecular Stille coupling, or vice versa.



Scheme 1 Retrosynthetic analysis

The synthesis of glycosyl fluoride **3** commenced with a known allyl alcohol (±)-**7** (Scheme 2).[6] Sharpless kinetic resolution of (±)-**7** gave *syn*-epoxy alcohol (+)-**8** in 33% yield and 99% ee, along with the starting material (–)-**7** (49%, 52% ee). After (+)-**8** was converted into *anti*-epoxy alcohol (+)-**9** via the Mitsunobu reaction,[7] transformation of (+)-**9** to cyclic carbamate (–)-**10** was achieved utilizing Roush's protocol.[8] Treatment of (+)-**9** with benzoyl isocyanate in CH_2Cl_2 followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave (–)-**10** in 89% yield through N→O rearrangement of the benzoyl group. N-Methylation of benzoate (–)-**10** using MeI and subsequent methanolysis gave the alcohol (+)-**11**. Pyran ring formation was accomplished by ozonolysis of (+)-**11** in MeOH followed by a reductive workup and acid treatment to give protected amino sugars **12** in 89% yield. To activate the anomeric position, a mixture of cyclic carbamates **12** was first converted to the corresponding thioglycosides using phenyl

trimethylsilyl sulfide (PhSTMS). Finally, a substitution reaction using *N*-bromosuccinimide (NBS) and (diethylamino)sulfur trifluoride (DAST) gave glycosyl fluoride **3** in 65% yield for two steps.[9]

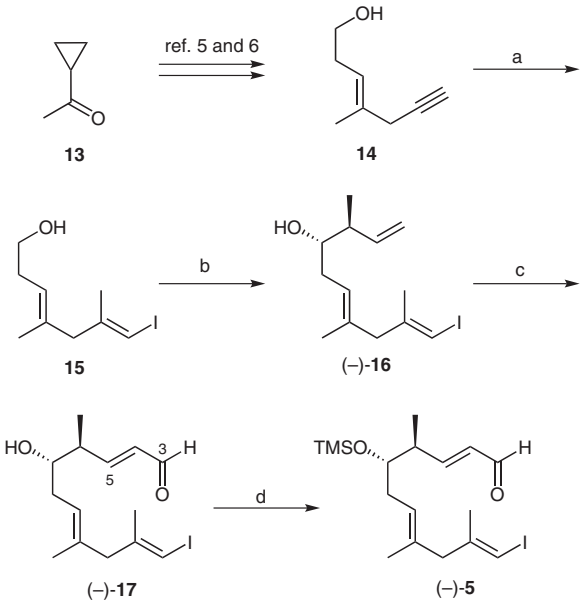


Scheme 2 Synthesis of glycosyl fluoride **3**. *Reagents and conditions*: (a) TBHP, (–)-DIPT, Ti(O*i*-Pr)$_4$, MS 3 Å, CH_2Cl_2, –20 °C, 32%, 99% ee; (b) (i) 4-$O_2NC_6H_4COOH$, Ph_3P, DIAD, THF, 0 °C, 100%; (ii) MeONa, MeOH, r.t., 84%; (c) (i) O=C=NBz, CH_2Cl_2, r.t., 100%; (ii) DBU, CH_2Cl_2, reflux, 90%; (d) (i) MeI, NaH, THF, r.t., 95%; (ii) MeONa, MeOH, r.t., 90%; (e) O_3, MeOH, –78 °C then DMS, PTSA, reflux, 89%; (f) (i) PhSTMS, TMSOTf, CH_2Cl_2, r.t., 91%; (ii) DAST, NBS, CH_2Cl_2, –15 °C, 71%.

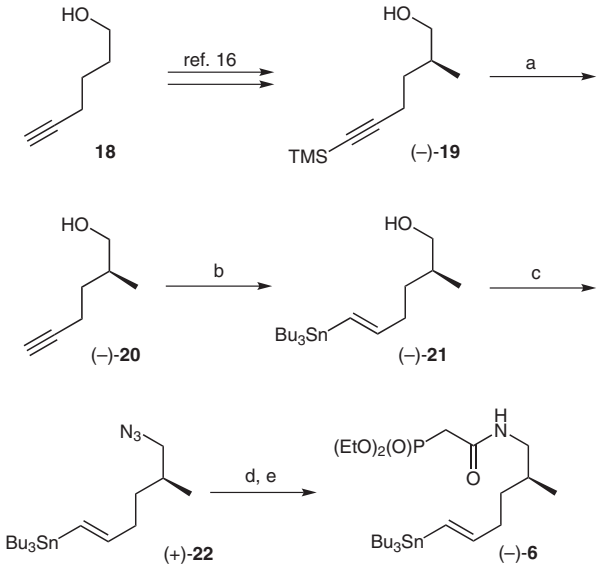
Synthesis of iodoenal **5** began from the known homoallyl alcohol **14**, which was prepared in four steps from cyclopropylmethylketone (**13**) using the Julia and Kakinuma procedure (Scheme 3).[3] Carboalumination of **14** in wet dichloromethane followed by iodination gave vinyliodide **15** in 64% yield. It should be noted that the carboalumination reaction did not give reproducible results in the absence of water.[10] Dess–Martin oxidation[11] of vinyliodide **15** followed by Brown asymmetric crotylboration[12] gave the homoallyl alcohol (–)-**16** in 47% overall yield and with high enantio- and diastereoselectivity (100% de, 94% ee).

Next, introduction of the C3–C5 enal moiety using a cross-metathesis reaction was examined. After considerable screening of cross-metathesis conditions (solvent, temperature, substrate concentration, and catalyst) and the metathesis partner (acrolein and methyl acrylate), we found that the reaction with acrolein in CH_2Cl_2 in the presence of a Hoveyda–Grubbs second-generation catalyst (H–G II catalyst)[13] gave reproducible results. However, the desired enal (–)-**17** was obtained in moderate yield along with byproducts, one of which was cyclopentenol produced by ring-closing metathesis (RCM) between the terminal and C9–C10 olefin. Silylation of (–)-**17** accomplished the synthesis of fragment **5** in 29% yield from (–)-**16**.

Preparation of phosphonate **6** commenced from the chiral known alcohol (–)-**19**[14] (prepared in five steps from **18**), as shown in Scheme 4. Removal of the trimethylsilyl group in (–)-**19**, followed by palladium-catalyzed hydrostannation of the resulting terminal alkyne (–)-**20** gave vinylstannane (–)-**21** in 74% yield with high regio- and stereoselectivity.[15] The minor *gem*-isomer could be easily removed after the intramolecular Stille coupling reaction (vide infra).

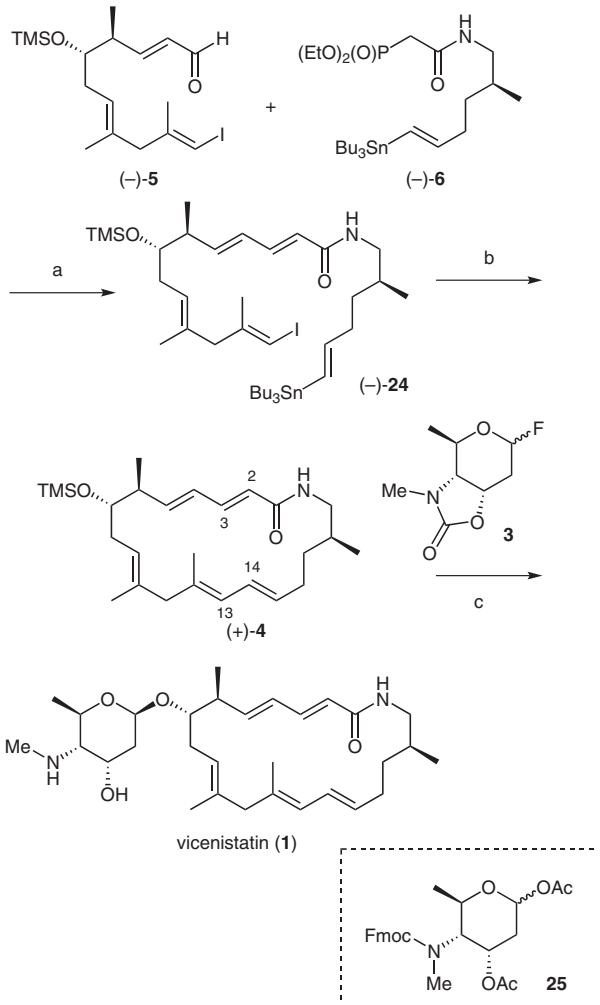


Scheme 3 Synthesis of fragment **5**. *Reagents and conditions*: (a) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2 (wet), 0 °C to r.t., then I_2, THF, 0 °C, 64%; (b) (i) Dess–Martin periodinane, CH_2Cl_2, r.t.; (ii) *cis*-2-butene, KO*t*-Bu, *n*-BuLi, (+)-Ipc$_2$BOMe, BF_3·OEt_2, THF, –78 °C, then MeOH, sat. aq $NaHCO_3$, 30% H_2O_2, –78 °C to 0 °C, 47%, 100% de, 94% ee; (c) acrolein, H–G II, CH_2Cl_2, r.t.; (d) TMSCl, Et_3N, CH_2Cl_2, r.t., 29% for 2 steps.



Scheme 4 Synthesis of fragment **6**. *Reagents and conditions*: (a) K_2CO_3, MeOH, r.t., 96%; (b) *n*-Bu_3SnH, $Pd_2(dba)_3$·$CHCl_3$, Cy_3P·HBF_4, *i*-Pr_2NEt, CH_2Cl_2, r.t., 74%, *gem*/*trans* = 1:20; (c) DPPA, DIAD, Ph_3P, THF, 0 °C to r.t., 82%; (d) (i) H_2 (balloon), Lindlar catalyst, quinoline, MeOH, r.t.; (ii) $(EtO)_2P(O)CH_2COOH$ **23**, EDCI, HOBt, Et_3N, CH_2Cl_2, r.t., 80%.

Vinylstannane (–)-**21** was converted into azide (+)-**22** under Mitsunobu conditions.[16] After the reduction of (+)-**22** using Lindlar catalyst, condensation of the resulting amine with diethylphosphonoacetic acid (**23**) furnished fragment (–)-**6**.



Scheme 5 Total synthesis of vicenistatin (**1**). *Reagents and conditions*: (a) **6**, KHMDS, THF, –78 °C, then **5**, 0 °C, 71%; (b) $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, *i*-Pr_2NEt, DMF, r.t., ca. 23%; (c) (i) **3**, TMSOTf, MS 4 Å, CH_2Cl_2, 0 °C; (ii) 5 M KOH, MeOH, r.t., 10% for **1**, 18% for the α-isomer (2 steps).

Having all fragments in hand, we then focused on construction of the macrocyclic lactam skeleton (Scheme 5). After several experiments, it was quickly recognized that intermolecular Stille coupling between iodide **5** and vinylstanane **6** was problematic. The reaction resulted in degradation of the starting material. In contrast, coupling of the two fragments using the HWE reaction proceeded without difficulty: phosphonate **6** was treated with KHMDS in THF at –78 °C, and the resultant phosphonate carbanion was successfully coupled with aldehyde **5** to give pentaene (–)-**24** in 71% yield. The intramolecular Stille coupling reaction of (–)-**24** proceeded under the Nicolaou conditions[17] [$Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, *i*-Pr_2NEt, DMF] to give the desired macrolactam **4** in modest yield.

Glycosylation of macrolactam **4** with glycosyl fluoride **3** using TMSOTf[18] as an activator proceeded to give an inseparable mixture of protected vicenistatin and its α-anomer. Although Kakinuma et al. have accomplished this glycosylation using glycosyl acetate **25** under the Mukaiyama conditions[3b,19] ($SnCl_4$, $AgClO_4$, MS 4 Å, CH_2Cl_2), the reaction could not be reproduced in our hands. Finally, removal of cyclic carbamate under the basic conditions proceeded to give vicenistatin (**1**) and its α-anomer in 10% and 18% yield for two steps, respectively. The spectroscopic data for the synthetic product were in good agreement with those for the natural product.[1]

In conclusion, we have accomplished a highly convergent total synthesis of vicenistatin (**1**). Glycosyl fluoride **3** was efficiently synthesized from allyl alcohol **7** in ten steps and 12% overall yield, and the synthesis of macrolactam **4** was achieved in a highly convergent manner (seven steps, 1.4% yield from **14**). Although several reactions, including fragment-coupling reactions and macrolactam formation, need to be optimized, synthetic efficiency and overall yield of the present synthesis are amenable to further SAR study and synthesis of the probe molecules for dissecting the mode-of-action of vicenistatin (**1**).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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