Enantioselective and Convergent Synthesis of the 20-Membered Lactam Aglycon of Vicenistatin Antitumor Antibiotic

Sir:

Vicenistatin (**1**), an antitumor antibiotic isolated from *Streptomyces* sp. HC-34, is unique in its structure which includes a 20-membered macrocyclic lactam aglycon and an aminosugar (vicenisamine).[1] The absolute stereochemistry of the aglycon has been determined as shown in structure (**2**), Scheme 1.[2] Its significant antitumor activities and unique structure prompted us to launch synthetic studies to clarify the chemical features essential to antitumor activity. The 20-membered macrolactam ring skeleton (**2**) has now been successfully synthesized and the absolute configuration has thus been verified.

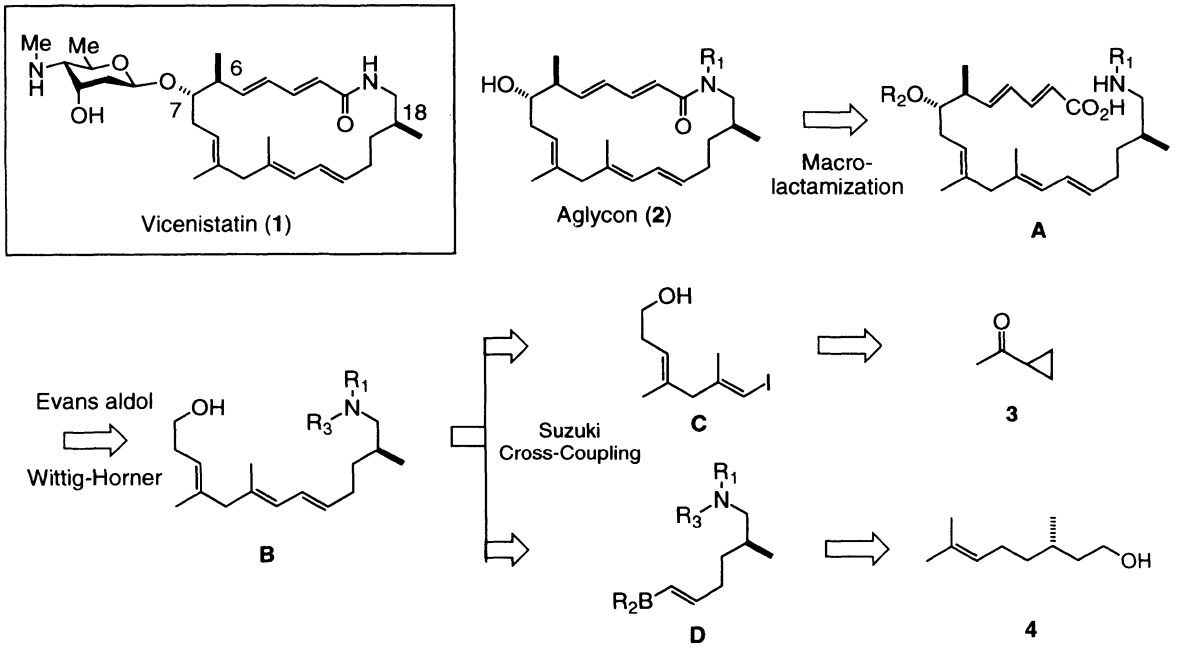
Our convergent synthetic plan, which should be flexible in view of possible structure modification, is shown in Scheme 1. We envisioned the final macrocyclization should be the lactam formation. The crucial precursor **A** can be synthesized from the triene-alcohol **B** by Evans asymmetric aldol reaction[3] and subsequent Wittig-Horner chain elongation, and the conjugated diene intermediate **B** can be stereoselectively constructed by Suzuki cross-coupling[4] of **C** and **D**. The vinyl iodide **C** is to be derived from cyclopropyl methyl ketone **3**, and the vinylboronate counterpart **D** may be synthesized from (*S*)-citronellol **4** *via* a corresponding acetylene **D'** (=**10b**).

The first stage of our work was the preparation of the two components, **C** (=**7b**) and **D'** (=**10b**), which are depicted in Scheme 2. The α-cyclopropyl alcohol **5**, which was obtained by Grignard reaction from **3**, was stereoselectively converted to (*E*)-homoallylic bromide **6a** (*E*:*Z*=*ca.* 14:1) by JULIA's method. The bromide **6a** was displaced with caesium acetate[5] to introduce an oxygen functional group. After deprotection of the acetyl group,[6] the resulting alcohol **6c** was converted to the silyl ether **6d**. Subsequently, (*E*)-vinyl iodide **7b** (=**C**) was synthesized by NEGISHI's method.[7]

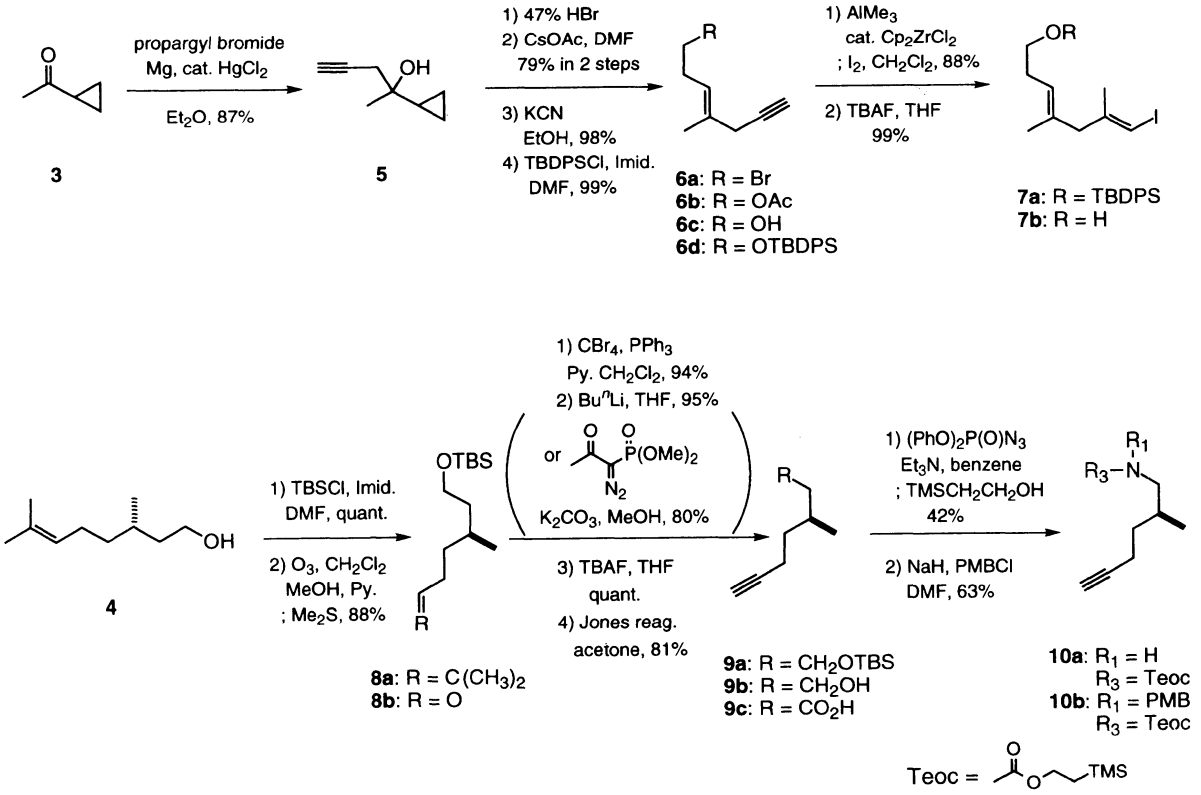
The vinylboronate counterpart **D** was synthesized from the corresponding acetylene **10b** prior to Suzuki coupling. Thus, ozonolysis of the TBS-protected **8a**, followed by COREY's[8] or BESTMANN's[9,10] procedure gave the acetylenic compound **9a**, which was then deprotected and oxidized to carboxylic acid **9c**. SHIOIRI's reagent[11] was used in the Curtius rearrangement to obtain the trimethylsilylethoxycarbonyl (Teoc) protected aminoacetylene **10a**, which was further converted to the *p*-methoxybenzyl (PMB) protected aminoacetylene **10b**.

The next stage of the synthesis was Suzuki coupling of these two components **7b** and **10b** (Scheme 3). The vinylboronate **D**, prepared from **10b** *in situ*, was reacted with the vinyl iodide **7b** in the presence of palladium catalyst to give the coupling product **11a** {^{1}H-NMR: δ

Scheme 1. Retrosynthetic analysis of the aglycon (**2**).



Scheme 2. Synthesis of coupling components (**7b** and **10b**).



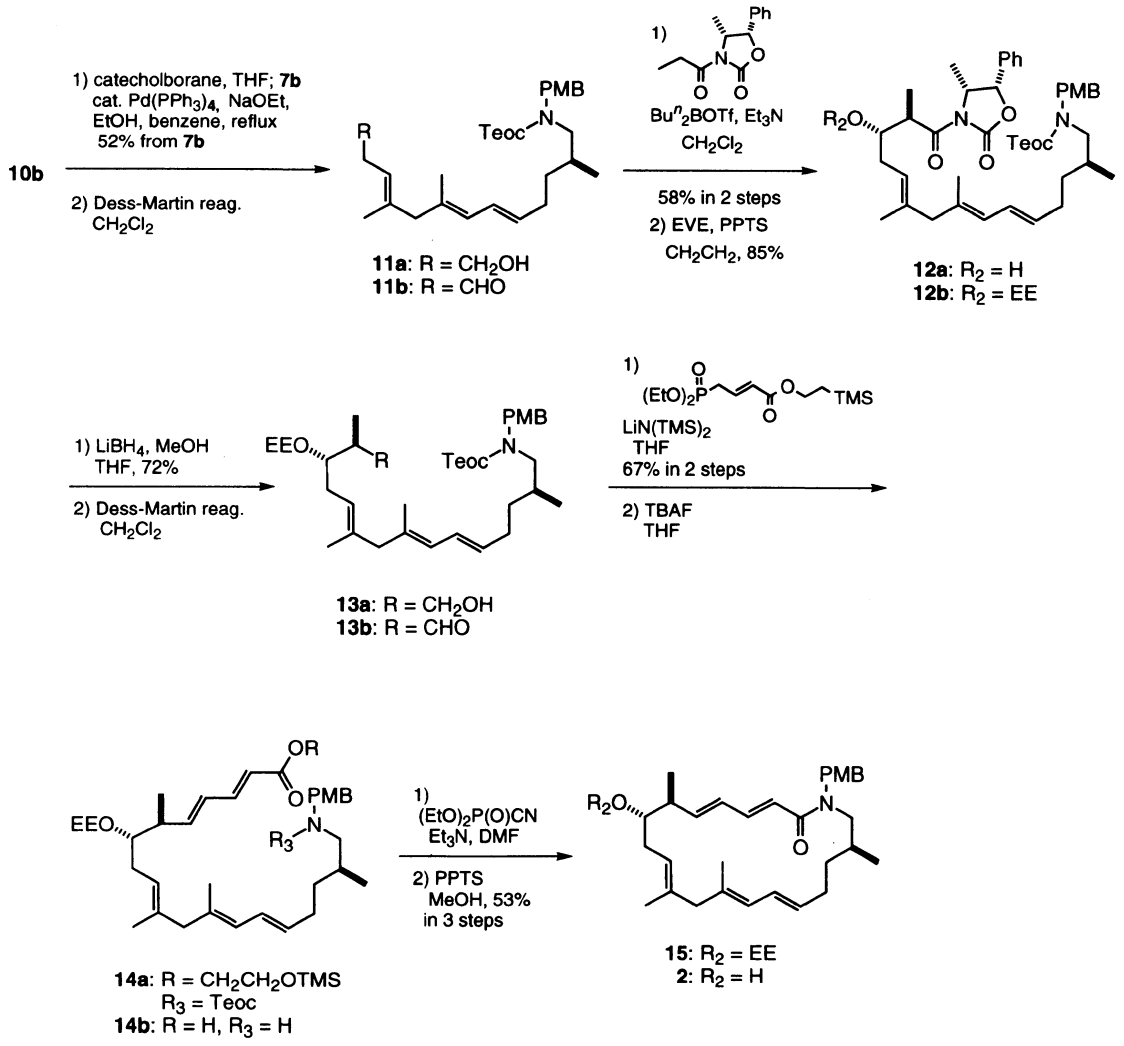
5.54 (ddd, J=6.8, 7.3, 14.6 Hz, H-15), 5.81 (d, J=10.7 Hz, H-13), 6.23 (dd, J=10.7, 14.6 Hz, H-14)} (vicenistatin numbering) in a moderate yield.

The most crucial stages were construction of the remaining two vicinal chiral centers, chain elongation and the final macrolactamization. The highly unstable aldehyde **11b**, which was obtained by Dess-Martin oxidation,[12] had to be immediately submitted to Evans aldol reaction to give **12a**. After protection of the resulting 7-hydroxy group as the 1-ethoxyethyl (EE) ether, the chiral auxiliary of **12b** was reductively removed by lithium borohydride to give the primary alcohol **13a**. The aldehyde **13b** obtained from **13a** was submitted to Wittig-Horner chain elongation to give the (*E,E*)-α,β-unsaturated ester **14a**, whose two silyl protective groups were simultaneously removed by tetra-*n*-butylammonium fluoride (TBAF) to give the aminocarboxylic acid **14b**, the precursor of the macrolactamization. The final cyclization was successful by SHIOIRI's method[13] to construct the macrolactam ring (H-11 geminal protons, which were observed as a singlet in the acyclic forms, were in contrast observed as a couple of AB-doublets: 2.57 and 2.72 J=14.1 Hz). The EE protective group of **15** was finally deprotected to give the N-PMB-aglycon **2**. Its specific rotation and all spectroscopic properties were identical with those of the naturally derived **2**, which was obtained from vicenistatin (**1**) in four steps: *i.e.* acidic hydrolysis; EE protection; N-PMB protection; EE deprotection.

In conclusion, we have successfully synthesized the

1. Compound **2**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.33 (dd, 1H, J=11.2, 14.5 Hz, 3-H); 7.19 {d, 2H, J=8.6 Hz, CC*H*CHC(OCH$_3$)C}, 6.84 {d, 2H, J=8.6 Hz, CCHC*H*C(OCH$_3$)C}, 6.31 (dd, 1H, J=11.3, 14.7 Hz, 14-H), 6.14 (d, 1H, J=14.5 Hz, 2-H), 6.10 (dd, 1H, J=11.2, 14.9 Hz, 4-H), 5.82 (dd, 1H, J=9.5, 14.9 Hz, 5-H), 5.75 (d, 1H, J=11.3 Hz, 13-H), 5.46 (ddd, 1H, J=6.9, 7.7, 14.7 Hz, 15-H), 5.24 (dd, 1H, J=6.8, 6.8 Hz, 9-H), 4.82 (d, 1H, J=14.6 Hz, one of benzyl-H), 4.40 (d, 1H, J=14.6 Hz, one of benzyl-H), 3.54~3.67 (m, 1H, 7-H), 3.79 (s, 3H, OCH$_3$), 3.27 (dd, 1H, J=7.1, 15.0 Hz, one of 19-H), 2.91 (dd, 1H, J=9.4, 15.0 Hz, one of 19-H), 2.73 (d, 1H, J=14.7 Hz, one of 11-H), 2.59 (d, 1H, J=14.7 Hz, one of 11-H), 2.08~2.44 (m, 5H, 6, 8 and 16-H), 1.87~2.05 (m, 1H, 18-H), 1.79 (s, 3H, 22-CH$_3$), 1.54 (s, 3H, 21-CH$_3$), 1.36~1.46 (m, 2H, 17-H), 1.12 (d, 3H, J=6.6 Hz, 20-CH$_3$), 0.92 (d, 3H, J=6.6 Hz, 23-CH$_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ=166.8, 158.8, 143.6, 142.9, 136.0, 135.0, 131.4, 130.0, 129.5, 129.4, 129.3, 128.0, 125.5, 119.6, 119.2, 113.8, 75.1, 55.2, 52.9, 51.4, 48.8, 43.3, 33.8, 33.4, 32.6, 30.4, 29.7, 18.3, 17.9, 17.6, 17.2; $[\alpha]_D^{20.5}$ = +34.5° (c=0.825, $CHCl_3$); Naturally derived: $[\alpha]_D^{19.5}$ = +27.3° (c=1.43, $CHCl_3$).

Scheme 3. Synthesis of the aglycon (**2**).



complete 20-membered macrocyclic lactam ring skeleton of vicenistatin (**1**). Further synthetic studies on the aminosugar (vicenisamine) and vicenistatin itself are now in progress.

Acknowledgements

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