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Synthesis of the C15–C27 portion of venturicidins: a formal total synthesis of venturicidin X

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Abstract—The C15–C27 portion of venturicidin X was prepared using substitution reactions of alkyl trifluoromethanesulfonates with a vinylmetal compound followed by homogeneous hydrogenation. Together with our previous synthesis of the C1–C14 portion of venturicidin X, a formal total synthesis of venturicidin X was completed.

The 20-membered macrolide antibiotics, venturicidins A and B, were isolated from several *Streptomyces* and their structures were elucidated by chemical degradations, spectroscopic investigations, and an X-ray crystallographic analysis.[1] In addition, venturicidin X, the aglycone of the venturicidins, was also isolated from *Streptomyces*.[2] In 1990, Akita, Oishi, and co-workers succeeded in synthesizing venturicidin X.[3] We have already reported the synthesis of the C1–C14 portion **1** (the bottom half) of venturicidin X (Fig. 1).[4] We now report in this letter the synthesis of the C15–C27 portion **2** (the upper half) of venturicidin X.[5,6] These two portions, **1** and **2**, are the intermediates of the Akita and Oishi synthesis of venturicidin X;[3] therefore, a formal total synthesis was completed.

During the course of our synthetic studies of macrolide antibiotics,[7] we developed the two-stage coupling process which consists of the addition reaction of chiral vinyllithium compounds to α-methyl-substituted aldehydes (e.g. **A**+**B**→**C**, Scheme 1) followed by the homogeneous hydrogenation of the *exo*-methylene group in

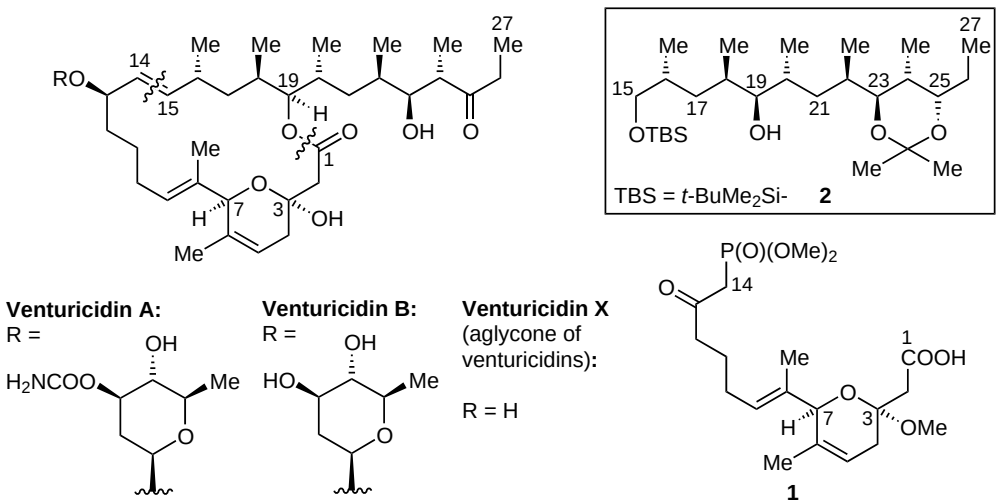

Figure 1.

Keywords: venturicidins; two-stage coupling process; substitution; hydrogenation.

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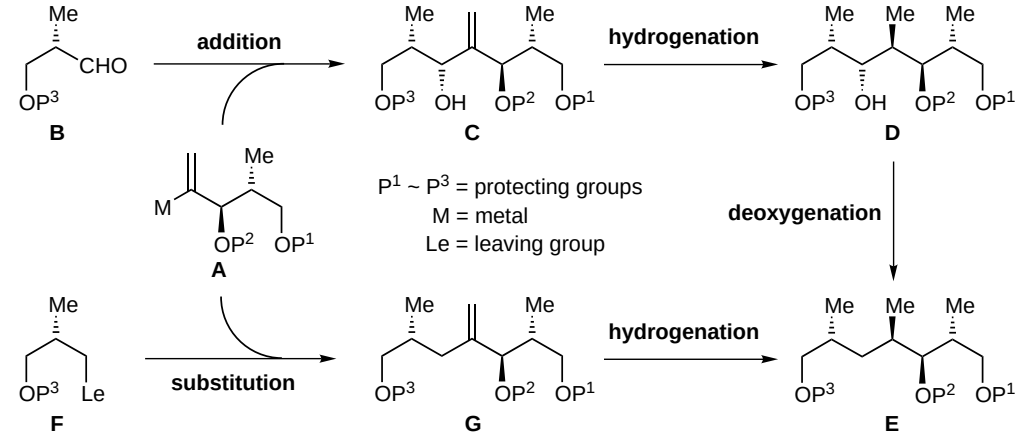
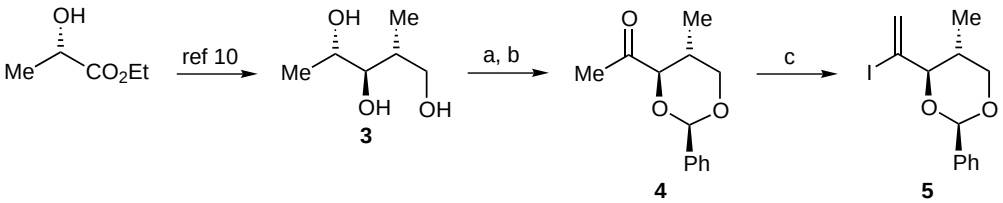


Scheme 1.



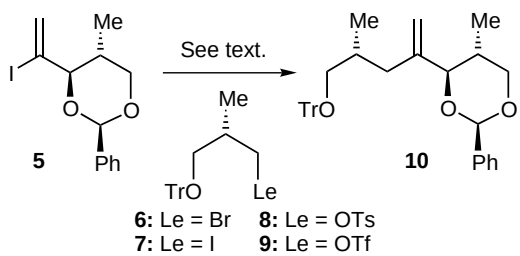
Scheme 2. *Reagents and conditions*: (a) $PhCH(OMe)_2$, CSA, DMF, rt, 1 h, 80%; (b) PCC, molecular sieves 3 Å powder, CH_2Cl_2, rt, 1 h, 99%; (c) $NH_2NH_2{\cdot}H_2O$, Et_3N, EtOH, 90°C, 0.5 h, then I_2, tetramethylguanidine, toluene, 0°C, 1 h, 63%.

the major Cram (*syn*) type of addition products with Wilkinson's catalyst (e.g. **C**→**D**, Scheme 1). In order to broaden the applicability of this two-stage coupling process, we realized the synthesis of the upper half of venturicidin X, which has the different protecting groups in **2**, starting from **B** (corresponding to the C15–C17 portion) by the consecutive coupling with **A** (corresponding to both the C18–C21 and C22–C25 portions) followed by a deoxygenation process (e.g. **D**→**E**, Scheme 1).[8] However, if the vinyllithium or vinylmetal compounds **A** react with alkyl halides or sulfonates **F** in an S_N2 manner,[9] the upper half of venturicidin X can be more directly obtained without the deoxygenation step (e.g. **A**+**F**→**G**→**E**, Scheme 1). We describe here the success of this strategy.

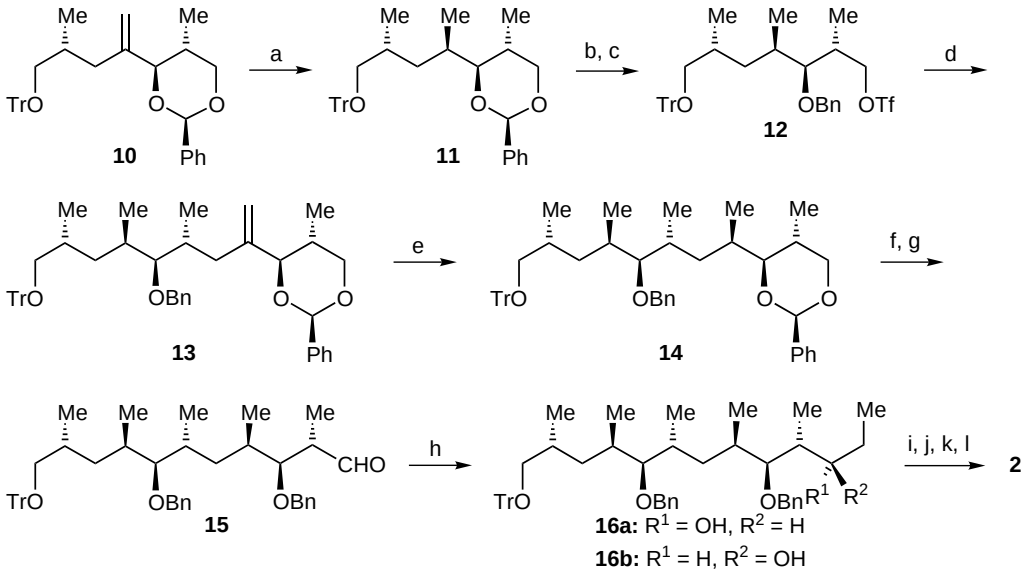
Vinyl iodide **5**, the precursor of the vinylmetal compound, was prepared as shown in Scheme 2. Triol **3**, which had been prepared from ethyl (*S*)-(−)-lactate by a literature procedure,[10] was selectively protected as its benzylidene acetal and the resulting alcohol was oxidized with PCC to give methyl ketone **4**.[11] This was converted through its hydrazone into vinyl iodide **5**[11] according to the improved procedure of Barton et al.[7a]

The key coupling reaction was extensively investigated (Scheme 3). Initially, we examined the coupling reaction of the vinyllithium compound derived from vinyl iodide **5** with alkyl halides, **6**[11,12] and **7**,[11,12] and sulfonates, **8**[11,12] and **9**[11,12] (Tf = trifluoromethanesulfonyl). After lithiation of **5** (in ether)[13] with 2.0 equiv. of *t*-BuLi in pentane (−78°C, 5 min),[14] each solution containing 1 equiv. of **6**, **7**, **8**, and **9** in ether was individually added; however, no coupling product was obtained at −78°C or decomposition occurred when the mixture was gradually warmed to rt. We next examined several additives (Bu_2Mg,[15] Et_2Zn, $ZnCl_2$, $MgBr_2{\cdot}OEt_2$, CuI, and CuCN for transmetallation and HMPA, TMEDA, and *N*,*N*′-dimethylpropyleneurea (DMPU) for co-solvent). We finally found the following procedure to be the best. After lithiation as described above, 1.0 equiv. of Et_2Zn in hexane was added and the mixture was warmed to −45°C. To this were added 6.0 equiv. of DMPU and 0.08 equiv. of Li_2CuCl_4[16] in THF; the mixture was then warmed to 0°C and to this was added 1.5 equiv. of **9** in ether. After 3 h at 0°C, usual work-up gave the desired coupling product **10** in 60% isolated yield.[17] This combination of reagents, vinyllithium, Et_2Zn, and copper, is, to the best of our knowledge, the first example to be used in the S_N2 type coupling reaction.[16,18–20]

Our next concern was homogeneous hydrogenation. All compounds used in the homogeneous hydrogenation stage of our two-stage coupling process[7] had a hydroxy

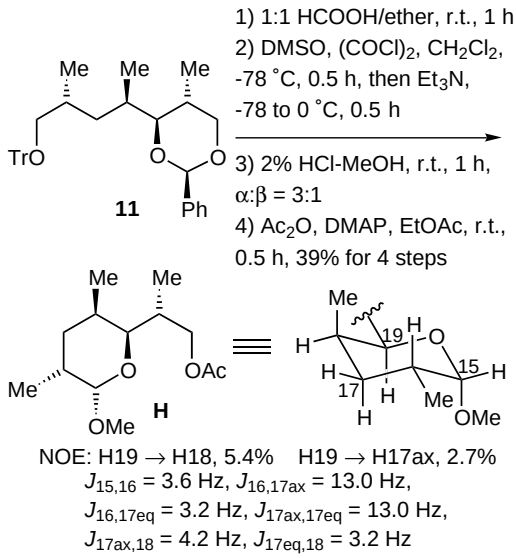


Scheme 3.



Scheme 4. *Reagents and conditions*: (a) H_2, [$ClRh(Ph_3P)_3$], benzene, rt, 12 h, 84%; (b) DIBAL, toluene, rt, 2 h, 87%; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, 5 min; (d) **5** (1.0 equiv. for **12**), *t*-BuLi, ether, −78°C, 5 min, then Et_2Zn, −45°C, then DMPU, Li_2CuCl_4, 0°C, then **12**, ether, 0°C, 3 h, 15% from the primary alcohol; (e) H_2, [$ClRh(Ph_3P)_3$], benzene, rt, 12 h, 82%; (f) DIBAL, toluene, rt, 2 h, 79%; (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, 0.5 h, then Et_3N, −78 to 0°C, 0.5 h; (h) EtMgBr, ether, 0°C, 0.5 h, 92% (**16a**:**16b** = 6:1); (i) 1% HCl–MeOH, rt, 3 h, 98%; (j) H_2, 10% Pd–C, EtOH, rt, 1 h, 82%; (k) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 3 h, 95%; (l) TBSCl, imidazole, CH_2Cl_2, rt, 1 h, 98%.

group in the allylic position (**C**, Scheme 1). Although the precise reaction mechanism has not been clarified, the hydroxy group might play a key role in the selectivity.[21] In the present case (**G**, Scheme 1), we had no confirmation of the acceptable selectivity. Fortunately, homogeneous hydrogenation of the coupling product **10** with hydrogen and Wilkinson's catalyst afforded **11**[11] in 84% yield as the sole product (Scheme 4). The configuration of the newly formed methyl-bearing carbon was verified by ^1H NMR analysis of the six-membered acetal **H** derived from **11** through the four-step sequence as shown in Scheme 5. Benzylidene acetal of **11** was selectively cleaved with DIBAL and the resulting primary alcohol was converted to the unstable triflate **12**. The second key coupling reaction of **12** with **5** was realized under the same conditions as described above; however, the yield of the coupling product **13**[11] was only 15%.[22] Although this coupling reaction was insufficient, in order to evaluate the overall synthetic strategy, it was decided to investigate the further transformation. Homogeneous hydrogenation of **13** cleanly proceeded to afford **14**[11] in 82% yield as the sole product. Reductive cleavage of benzylidene acetal in **14** with DIBAL and the resulting primary alcohol was oxidized under the Swern conditions, giving aldehyde **15**. Addition of ethylmagnesium bromide to **15** afforded a 6:1 mixture of the Felkin–Anh alcohol **16a**[11] and its epimer **16b**[11] in 73% combined yield from **14**. The major alcohol **16a** was transformed to the C15–C27 segment **2** through the four-step sequence in 75% overall yield. The obtained synthetic **2** was identical with the reported one[3b,5b] based on a spectroscopic comparison;[23] the configurations of the C22 and C25 positions were confirmed at this stage. Together with our previous synthesis of the C1–C14 portion **1** of venturicidin X,[4] a formal total synthesis of venturicidin X was thus completed.



Scheme 5.

Although there is still room for improvement in the coupling reaction described herein, we believe this reaction would be an alternative to the Negishi[19] and Jackson[20] cross-coupling reactions.

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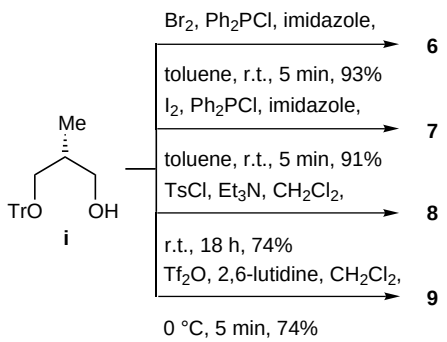
11. Satisfactory analytical data (NMR and IR spectra, elemental analyses and/or HRMS, optical rotations) were obtained for all new compounds.
12. Compounds **6** and **7** were prepared from the known alcohol **i**[7a] by the literature procedure (Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126–6130). Compounds **8** and **9** were prepared from **i**[7a] as shown in Scheme 6.



Scheme 6.

13. In THF, significant decomposition occurred.
14. More than 95% lithiation was confirmed by a D_2O quenching experiment.
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17. Instead of triflate **9**, iodide **7** was recovered from the reaction mixture. This indicates that LiI, which exists in the reaction mixture, competitively attacks triflate **9**. A separate experiment showed that iodide **7** is less reactive than triflate **9**. In order to prevent this exchange, the vinyl tributyltin equivalent of **5** was prepared and subjected to the lithiation conditions; however, all efforts resulted in failure.
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22. The low yield of **13** was due to not only the inertness of the iodide equivalent of **12**, which was derived from **12** and in-situ contaminated LiI, but also the instability of **12**.
23. Compound **2**: $[\alpha]_D^{24}$ +33.6 (*c* 2.09, $CHCl_3$) [lit.,[3b] $[\alpha]_D^{20}$ +32.7 (*c* 2.14, $CHCl_3$). lit.,[5b] $[\alpha]_D^{20}$ +32.8 (*c* 2.10, $CHCl_3$)]. IR (neat): 3440, 2960, 2930, 2880, 2860, 1470, 1460, 1380,

1250, 1220, 1180, 1150, 1100, 1020, 980, 880, 840, 780, and 760 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (6H, s), 0.80–0.95 (18H, m), 0.89 (9H, s), 1.08 (1H, ddd, $J=13.2$, 9.2, and 4.4 Hz), 1.22 (1H, ddd, $J=13.2$, 9.8, and 3.0 Hz), 1.30 (3H, s), 1.32 (3H, s), 1.33–1.48 (3H, m), 1.53 (1H, ddd, $J=13.0$, 10.0, and 2.8 Hz), 1.59–1.83 (6H, m), 3.08–3.17 (2H, m), 3.36 (1H, dd, $J=9.6$ and 6.4 Hz), 3.44 (1H, dd, $J=9.6$ and 5.8 Hz), 3.63 (1H, ddd, $J=8.6$, 4.4, and 4.4 Hz) [after D_2O addition, the peaks of 1.59–1.83 (6H, m) and 3.08–3.17 (2H, m) change to those of 1.60–1.83 (5H, m) and 3.12 (2H, dd, $J=7.0$ and 4.0 Hz), respectively]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.35, 10.53, 12.65, 12.94, 14.67, 16.00, 16.55, 18.34, 23.64, 25.36, 25.96, 32.08, 33.10, 33.46, 33.51, 35.12, 36.19, 37.67, 68.97, 71.21, 79.25, 80.01, 100.14. HRMS (FAB+) calcd for $C_{27}H_{56}NaO_4Si$ $(M+Na)^+$: 495.3846. Found: 495.3864.