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Synthesis of C15–C27 segment of venturicidine X by utilizing desymmetrization protocol

J. S. Yadav *, Sk. Samad Hossain, Debendra K. Mohapatra

Organic Chemistry Division-I, Indian Institute of Chemical Technology (CSIR), Hyderabad 500 007, India

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ABSTRACT

We have achieved the synthesis of C15–C27 fragment of venturicidine X using desymmetrization protocol, substrate-controlled Grignard reaction, Barton–McCombie reaction, Sharpless epoxidation, and TBSOTf-mediated rearrangement to produce the aldol product through a non-aldol route as the key step following 23 longest linear sequences with 6.4% overall yield starting from a known intermediate **11**.

Venturicidines A, B, and its aglycone venturicidine X, 20-membered macrolide antibiotics, were isolated from several *streptomyces*.[1] Their structures and absolute configurations (Fig. 1) were elucidated by chemical degradations, spectroscopic correlation, and X-ray crystallographic analysis.[2] They exhibit strong activity against a number of plant pathogenic fungi and mitochondrial H^+ATPase.[3] In 1990, Akita et al. accomplished the first total synthesis and determination of absolute stereochemistry of the aglycone of venturicidines A and B.[4] Encouraged by the interesting chemical structure combined with remarkable biological activities, we decided to apply our developed desymmetrization protocol and herein we present a highly stereocontrolled synthesis of C15–C27 segment[4b,5] of venturicidine X.

Retrosynthetic analysis revealed that venturicidine X can be divided into two major segments C1–C14 (**2**) and C15–C27 (**3**), which could be coupled by esterification followed by Wittig–Horner condensation. Fragment **3** would be obtained from the intermediate **4** by Sharpless asymmetric epoxidation followed by TBSOTf-mediated rearrangement to produce the aldol product by a non-aldol route as the key reaction. Intermediate **4** would be obtained from **5** following standard reaction procedure. The intermediate **5** could be obtained from a known bicyclic lactone **6** employing acid-catalyzed methanolysis and substrate-controlled Grignard reaction as key steps. The bicyclic lactone **6** would be obtained by utilizing

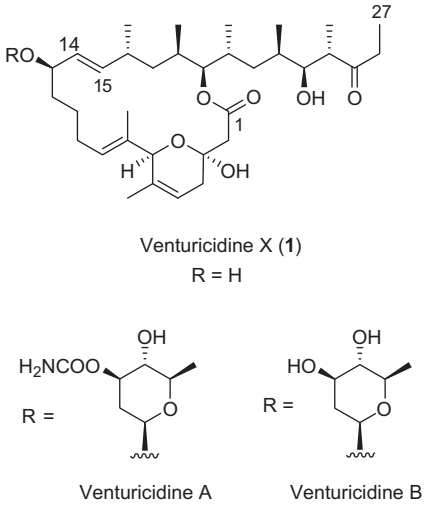

Figure 1. Structures of venturicidines A, B, and its aglycone venturicidine X.

desymmetrization technique to create six contiguous chiral centers (Scheme 1).

The *exo*-alkylated lactone **6**[6] was obtained by the following sequence, Zn–Cu couple-mediated (−10 °C) [4+3] cycloaddition reaction between 2,4-dibromopentan-3-one and furan to form 2,4-dimethyl-8-oxabicyclo-[3.2.1]-oct-6-ene-3-ones **7**,[7] DIBAL-H reduction **8**, benzyl protection **9**, asymmetric hydroboration **10**, PCC mediated oxidation, Bayer–Villiger reaction,[8] and alkylation

* Corresponding author. Tel.: +91 40 27193128; fax: +91 40 27160387.
E-mail addresses: yadavpub@iict.res.in (J.S. Yadav), mohapatra@iict.res.in (D.K. Mohapatra).

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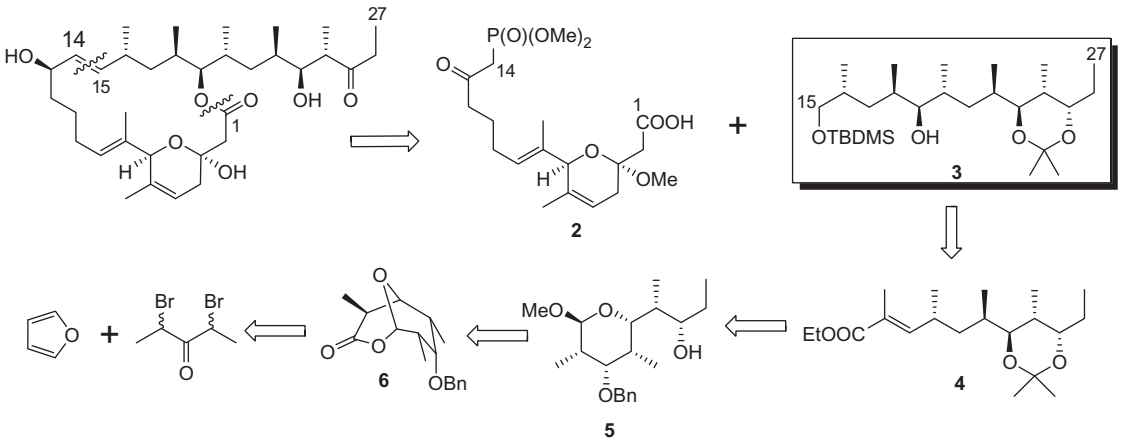


Scheme 1. Retrosynthetic analysis of venturicidine X.

6. Acid-catalyzed methanolysis,[9] lithium aluminum hydride (LAH)-mediated reduction, and IBX[10]-mediated oxidation afforded the aldehyde **11**.[11] Substrate-controlled Grignard reaction[12] with ethyl magnesium bromide in THF afforded the desired Felkin–Anh[13] alcohol **5**[14] (89%) as the major product (93:7 by HPLC) (Fig. 2). The absolute stereochemistry of the newly generated chiral center was confirmed in the later stage of the synthesis.[15] Acetylation of **5** with acetic anhydride furnished **12** (95%) (Scheme 2).

Compound **12** upon treatment with 60% aqueous acetic acid at 60 °C followed by TEMPO-BAIB-mediated oxidation[16] afforded **13** (76% over two steps). The axial methyl center was isomerized to equatorial using DBU as the base to obtain **14** and upon treatment with LAH in THF provided triol **15** (80% over two steps). Acetonide protection of **15** followed by catalytic hydrogenation using Pd–C afforded **16**[17] (76% over two steps). The primary hydroxyl group was selectively protected with TBDMSCl and imidazole to afford **17** (90%) and the secondary hydroxyl group was converted to its xanthate derivative **18** (87%) which on subsequent treatment with Bu_3SnH[18] in the presence of a catalytic amount of AIBN in refluxing benzene afforded **19** (92%). Desilylation of the primary hydroxyl group using TBAF in THF at room temperature afforded **20** (91%) (Scheme 3).

IBX oxidation of **20** in DMSO and THF furnished aldehyde, which on Wittig homologation with $Ph_3P{=}C(Me)COOEt$ in refluxing benzene afforded α,β-unsaturated ester **4** (77% over two steps) favoring the desired *E*-isomer. DIBAL-*H* reduction of the ester afforded the corresponding allylic alcohol. Sharpless asymmetric epoxidation[19] proceeded efficiently to produce epoxide **21** (78% over two steps) which upon treatment with TBSOTf and *N,N*-diisopropylethylamine furnished a rearranged aldehyde **22** (76%) with good selectivity.[20] Wittig homologation of aldehyde **22** with $Ph_3P{=}CHCOOEt$ in refluxing benzene (89%) followed by catalytic hydrogenation with Pd–C afforded **23**[21] (96%) and further lactonization in the presence of PPTS in CH_2Cl_2/MeOH (10:1) furnished **24** (86%). Diastereoselective methylation[22] of lactone **24** with LDA in the presence of MeI at −78 °C provided **25** (85%). Reduction of lactone **25** with LAH in THF afforded diol which on selective protection with TBDMSCl and imidazole afforded the desired C15–C27 segment **3** of venturicidine X in 95% yield (Scheme 4). The spectral and analytical data of **3**[23] were identical with the literature reported values.

In conclusion, we have achieved the synthesis of C15–C27 polyketide back bone of venturicidine X using desymmetrization protocol, substrate-controlled Grignard reaction, Barton–McCombie reaction, Wittig reaction, Sharpless epoxidation, and TBSOTf-mediated rearrangement to produce an aldol product through a non-aldol route as the key step following 23 longest liner sequences with 6.4% overall yield starting from a known intermediate **11**.

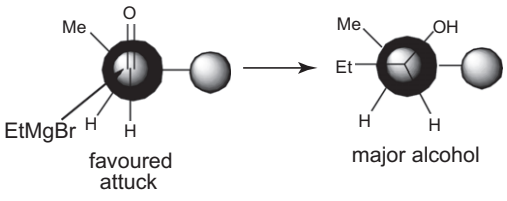
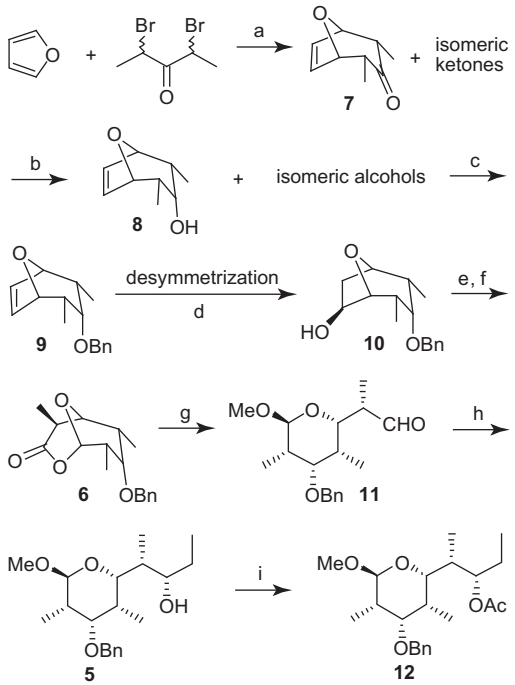
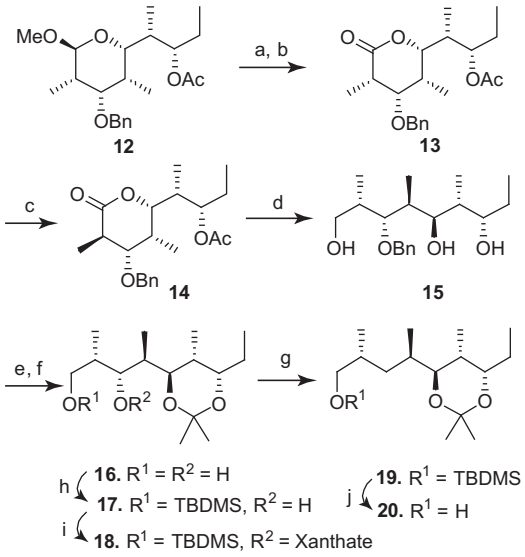


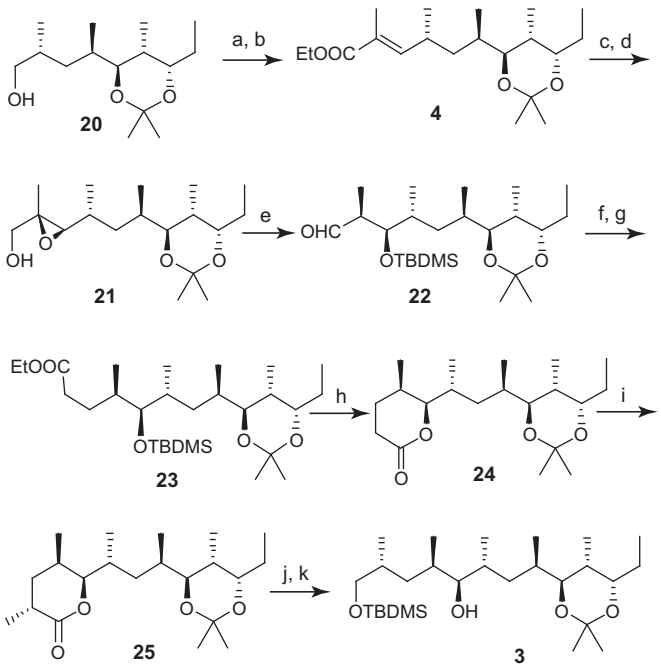
Figure 2. Felkin–Anh model for the formation of **5**.



Scheme 2. Reagents and conditions: (a) Zn–Cu couple, DME, −10 °C, 6 h, 82%; (b) DIBAL-H, CH_2Cl_2, −10 °C, 1 h, 74% (required product); (c) NaH, BnBr, THF, 50 °C, 94%; (d) $(-)$-$(Ipc)_2BH$, THF, −20 °C, 5 days, 92%; (e) (1) PCC, CH_2Cl_2, rt, 3 h, 90%; (2) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 90%; (f) LDA, MeI, THF, −78 °C, 1 h, 94%; (g) (1) LAH, THF, 0 °C to rt, 12 h, 89%; (2) IBX, DMSO, THF, rt, 6 h, 95%; (h) EtMgBr, THF, −78 °C, 1 h, 89%; (i) Ac_2O, Et_3N, CH_2Cl_2, rt, 1 h, 95%.



Scheme 3. Reagents and conditions: (a) 60% AcOH/H_2O, 60 °C, 3 h, 82%; (b) TEMPO, BAIB, CH_2Cl_2, rt, 3 h, 93%; (c) cat. DBU, CH_2Cl_2, 4 h, 90%; (d) LAH, THF, rt, 2 h, 89%; (e) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt, 6 h, 85%; (f) H_2, Pd–C (10%), hexane, 12 h, 89%; (g) TBDMSCl, Imid, CH_2Cl_2, 2 h, 0 °C, 90%; (h) NaHMDS, CS_2, MeI, THF, −78 °C, 1 h, 87%; (i) Bu_3SnH, AIBN, PhH, 80 °C, 3 h, 92%; (j) TBAF, THF, rt, 2 h, 91%.



Scheme 4. Reagents and conditions: (a) IBX, DMSO, THF, rt, 2 h, 92%; (b) $Ph_3P{=}C(Me)COOEt$, benzene, 80 °C, 3 h, 84%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 93%; (d) ^tBuOOH, $Ti(O^iPr)_4$, D-(−)-DET, 4 Å MS, −20 °C, 12 h, 84%; (e) TBSOTf, DIPEA, 4 Å MS, −40 °C, 76%; (f) $Ph_3P{=}CHCOOEt$, benzene, 80 °C, 4 h, 89%; (g) H_2, Pd–C (10%), EtOAc, 3 h, 96%; (h) PPTS, CH_2Cl_2/MeOH (10:1), 0 °C, 5 h, 86%; (i) LDA, MeI, −78 °C, 1 h, 85%; (j) LAH, THF, 0 °C to rt, 1 h, 92%; (k) TBDMSCl, Imid, CH_2Cl_2, 0 °C, 1 h, 95%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.148.

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14. *Spectral and analytical data of* **5**: $[\alpha]_D^{27}$ +37.0 (*c* 1.4, $CHCl_3$); IR (neat): ν_{max} 3498, 2969, 2933, 2851, 1459, 1354, 1259, 1209, 1183, 1132, 1078, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5H), 4.51 (s, 1H), 4.49 (s, 2H), 3.87–3.77 (m, 3H), 3.36 (s, 3H), 2.18 (m, 1H), 2.06 (tdd, *J* = 12.2, 6.7, 2.6 Hz, 1H), 1.82 (tdd *J* = 13.9, 6.9, 1.8 Hz, 1H), 1.70 (d, *J* = 5.6 Hz, 1H), 1.57–1.36 (m, 2H), 1.05 (d, *J* = 7.5 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 128.2, 127.3, 127.1, 104.8, 75.3, 73.4, 70.9, 69.3, 55.4, 38.2, 36.5, 33.4, 26.9, 13.2, 10.9, 9.3, 7.7; HRMS: *m*/*z* calcd for $C_{20}H_{32}O_4$ 337.2378; found 337.2368.
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17. *Spectral and analytical data of* **17**: $[\alpha]_D^{27}$ −5.3 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 3522, 2933, 2960, 1463, 1380, 1253, 1224, 1154, 1088, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74–3.56 (m, 5H), 3.08 (d, *J* = 2.83 Hz, 1H), 1.88–1.64 (m, 2H), 1.61 (tdd, *J* = 14.7, 6.7, 2.07 Hz, 1H), 1.50–1.24 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H), 0.98–0.86 (m, 6H), 0.90 (s, 9H), 0.84 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.6, 75.0, 74.4, 71.6, 68.1, 38.6, 37.3, 35.9, 26.1, 25.4, 23.9, 23.9, 18.5, 12.4, 11.1, 10.7, 9.9, −5.3; ESIMS: *m*/*z* $[M+Na]^+$ 412.
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21. *Spectral and analytical data of* **23**: $[\alpha]_D^{27}$ +21.7 (*c* 1.7, $CHCl_3$); IR (neat) ν_{max} 2961, 2933, 2883, 1736, 1462, 1377, 1253, 1224,1176, 1093, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.2 Hz, 2H), 3.58 (dt, *J* = 9.3, 5.2 Hz, 1H), 3.30 (dd, *J* = 5.2, 3.1 Hz, 1H), 3.06 (dd, *J* = 7.2, 3.1 Hz, 1H), 2.35–2.18 (m, 2H), 1.76–1.36 (m, 8H), 1.35–1.28 (m, 1H), 1.27 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.06–0.98 (m, 1H), 0.90 (s, 9H), 0.94–0.79 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 100.0, 79.9, 79.0, 71.1, 60.2, 36.7, 36.5, 35.6, 34.8, 33.7, 32.7, 30.5, 26.2, 25.3, 23.6, 18.4, 16.1, 14.2, 13.5, 12.5,10.5, 1.0, −3.8; ESIMS: *m*/*z* $[M+Na]^+$ 523.
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23. *Spectral and analytical data of* **3**: $[\alpha]_D^{27}$ +35.0 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3503, 2958, 2925, 2855, 1462, 1378, 1251, 1225, 1177, 1153, 1094, 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.63 (ddd, *J* = 9.1, 4.8, 4.6 Hz, 1H), 3.44 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.37 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.16–3.11 (m, 2H), 1.81–1.51 (m, 7H), 1.48–1.33 (m, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.27–1.17 (m, 1H), 1.10 (ddd, *J* = 13.4, 9.5, 4.4 Hz, 1H), 0.90 (s, 9H), 0.94–0.82 (m, 18H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 100.2, 80.0, 79.2, 71.2, 69.0, 37.6, 36.1, 35.0, 33.5, 33.4, 33.1, 32.0, 25.9, 25.3, 23.6, 18.3, 16.5, 16.0, 14.7, 12.9, 12.7, 10.5, -5.3; ESIMS: *m*/*z* $[M+Na]^+$ 496.