# Synthesis of the Racemic $C_{15}$-$C_{23}$ Segment of the Venturicidins

S. Woo, B.A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

Fax 1-403-284-1372; E-mail: keay@acs.ucalgary.ca

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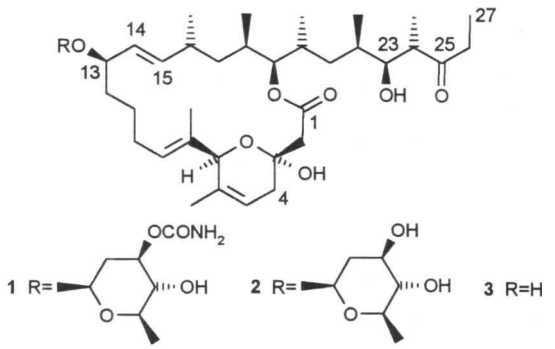
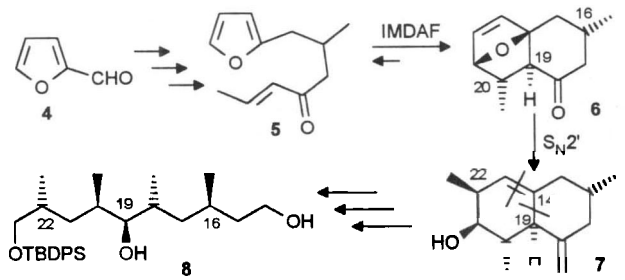
**Abstract:** The (±)-$C_{15}$-$C_{23}$ portion of the venturicidins is synthesized stereoselectively in 17 steps from 2-furaldehyde in an overall yield of 7%.

Venturicidin A (**1**) and B (**2**) have been isolated from soil actinomycetes (1961)[1] and *Streptomyces aureofaciens* (1968),[2] respectively, while recently the aglycone, venturicidin X (**3**) was found in an unidentified *Streptomyces* species in 1994 (Scheme 1).[3] All three compounds are active against a variety of phytopathogenic fungi, including barley, cucumber, and apple mildew, apple scab, and grey mould,[1-3] and inhibit the ATP synthetase system of mitochondria.[4] Only one synthesis of the aglycone **3** has been reported to date by Akita *et al.* in 1990;[5] however, syntheses of both the $C_1$-$C_{14}$[6] and $C_{15}$-$C_{27}$[7] segments of the venturicidins have been reported recently. We herein report a racemic synthesis of the $C_{15}$-$C_{23}$ fragment of the venturicidins.

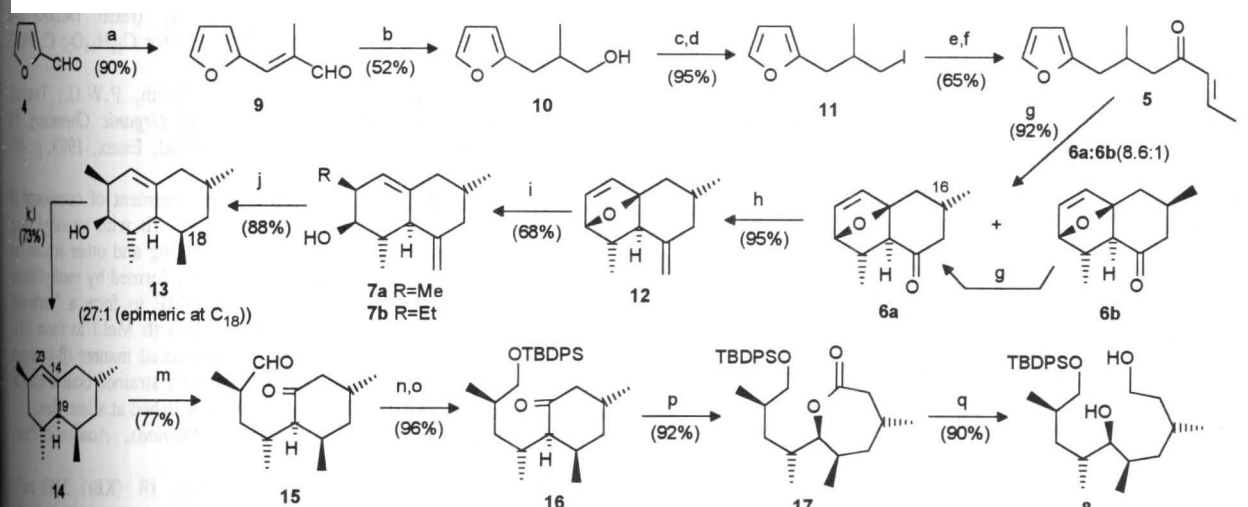



**Scheme 1**

We have been investigating the intramolecular Diels-Alder reaction with furan dienes[8] and the $S_N2'$ ring opening of the resultant oxatricyclo adducts as a combined strategy for controlling relative stereochemistry.[9] Thus, our strategy towards the $C_{15}$-$C_{23}$ segment **8** (Scheme 2) involved a thermodynamically controlled diastereoselective intramolecular Diels-Alder reaction with a furan diene (IMDAF) to establish the relative stereochemistry between $C_{16}$, $C_{19}$, and $C_{20}$ (**5**→**6**, Scheme 2).[8c] The $C_{22}$ methyl group was introduced via an $S_N2'$ ring opening of the oxatricyclo system after conversion of the ketone into a double bond (**6**→**7**).[9] After some functional group interconversions, the resultant bicyclo system was cleaved at the $C_{14}$-$C_{22}$ and $C_{14}$-$C_{19}$ bonds to provide **8** containing the correct relative stereochemistry for the $C_{15}$-$C_{23}$ fragment of the venturicidins.




**Scheme 2**



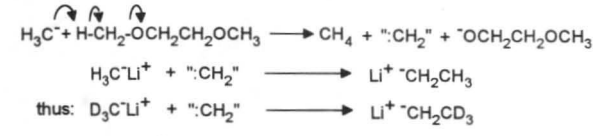

**Reagents:** a) EtCHO, NaOH/$H_2O$, 10 min, r.t.; b) Na.Hg, EtOH, 5.5 h, r.t.; c) TsCl, DMAP, $Et_3N$, $CH_2Cl_2$, 14 h, r.t.; d) NaI, acetone, 16 h, reflux; e) 2.2 eq *t*-BuLi, $Et_2O$, -78°C, 5 min; then crotonaldehyde; f) $Ag_2CO_3$/Celite, benzene, 16 h, reflux; g) $MeAlCl_2$, $CH_2Cl_2$, -78°C, 5 h; h) $Ph_3PCH_3Br$, *n*-BuLi, 0°C (5 min), r.t. (30 min), add **6a**, 2.5 h, r.t.; i) 30 eq. MeLi, DME, 24 h, r.t.; j) $H_2$ (1 atm), $PtO_2$, EtOH/benzene, 2 h, r.t.; k) KH, THF, 0°C to r.t., 2h; then $CS_2$, 2h, then MeI, 12 h; l) TTMSS, AIBN, Toluene, 90°C, 2h; m) $RuO_2 \cdot H_2O$/$NaIO_4$ added to **14** in 9:1 acetone:$H_2O$ and worked up immediately; n) $NaBH_4$, EtOH:$CH_2Cl_2$, -78°C, 2 h; o) TBDPSCl, DMAP, $CH_2Cl_2$, 12 h, r.t.; p) MCPBA, $NaHCO_3$, $CH_2Cl_2$, 76 h, r.t.; q) LAH, $Et_2O$, 1h, r.t.

**Scheme 3**

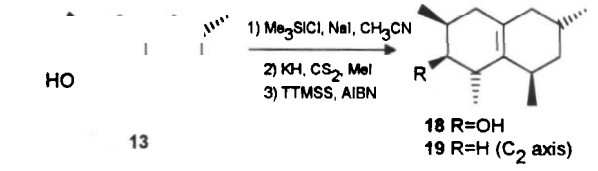
To this end, the IMDAF precursor **5** was prepared as follows. An aldol condensation[10] between 2-furaldehyde (**4**) and propanal produced aldehyde **9** (90%, Scheme 3). Both the double bond and carbonyl in **9** were reduced with sodium amalgam in ethanol to provide alcohol (±)-**10** (65%),[11] which was converted in two steps to the iodide **11** (95% from **10**).[8d] Halogen-metal exchange of **11** at -78°C with *t*-butyllithium in ether, followed by a quench of the anion with crotonaldehyde[8d] and Fetizon's oxidation[12] of the resulting allylic alcohol, provided **5** (65% from **11**).

The IMDAF reaction of **5** proceeded smoothly to give an 8.6:1 ratio of diastereomers **6a**[13] and **6b** in 92% combined yield when **5** was treated with 10 mol% $MeAlCl_2$ in $CH_2Cl_2$ at -78°C for 5h. The diastereomers were easily separated and found to be epimeric at $C_{16}$ (venturicidin numbering). Since the IMDAF reaction was under thermodynamic control,[8c] the minor isomer **6b** was recycled in subsequent IMDAF reactions, thereby increasing the overall stereoselectivity of the IMDAF reaction. Wittig reaction[14] of **6a** provided adduct **12** (95%), which when treated with excess methyllithium in DME[8c] provided the ring opened product **7a** (68%) and the unexpected ethyl containing compound **7b** (11%).[15] A highly chemoselective catalytic hydrogenation[16] of the exocyclic double bond in **7a** ($H_2$, $PtO_2$) gave a 27:1 mixture of compounds (**13**[17] (88%)) which were epimeric at $C_{18}$.[18] A Chatgilialoglu[19] modified Barton[20] deoxygenation of the hydroxyl group in **13** provided **14** in 73% yield.

With **14** in hand, our attention turned to examining various methods for cleaving the $C_{14}$-$C_{23}$ and $C_{14}$-$C_{19}$ bonds in **14**. Cleavage of the $C_{14}$-$C_{23}$ bond was more difficult than expected; reductive ozonolysis[21] resulted in complex mixtures, while $NaIO_4$ with catalytic amounts of $OsO_4$,[22] or $KMnO_4/(Et)_3BnN^+Cl^-/CH_2Cl_2$[23] provided only starting material. Oxidative cleavage of the double bond was achieved with $RuO_4$ generated *in situ* by adding catalytic $RuO_2{\cdot}H_2O$ and two equivalents of $NaIO_4$;[24] however, the yield of compound **15** varied from run to run. Consistent yields of aldehyde **15**[25] (77%) were obtained when a stoichiometric amount of $RuO_4$ in $CCl_4$ was added to **14** in acetone.[26] Since compound **15** was quite unstable, it was decided to reduce and protect the aldehyde in **15** so that conditions could be found that would cleave the $C_{14}$-$C_{19}$ bond. Thus, the aldehyde in **15** was selectively reduced to an alcohol[27] and subsequently protected as a TBDPS ether[28] to provide **16** (96% from **15**). A Baeyer-Villiger reaction[29] on **16** provided lactone **17** (63%, 92% based on recovered **16**), with retention of stereochemistry at $C_{19}$, which was reduced with $LiAlH_4$ in ether to provide (±)-**8**[30] (90%).




**Scheme 4**




**Scheme 5**

We have shown that compound (±)-**8** can be prepared with high stereoselectivity in 17 steps from 2-furaldehyde (**4**) in 7% overall yield. Compound **8** contains the correct relative stereochemistry found in the $C_{15}$-$C_{23}$ segment of the venturicidins and illustrates that a combined IMDAF-$S_N2'$ ring opening strategy is useful for controlling the relative stereochemistry between 4-5 centres. Work is continuing to prepare compound **8** asymmetrically[8c] and to finish the synthesis of venturicidin X (**3**).

**Acknowledgements**

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**References and Notes**

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(13) Compound (±)-**6a**: mp 49-50°C; IR (neat) 1707 cm⁻¹; $^1$H-NMR (200 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=7.0 Hz), 1.[illegible] (d, 3H, J=6.0 Hz), 1.70 (d, 1H, J=4.0 Hz), 1.90 (dd, J=11.8 and 14.6 Hz), 2.02-2.17 (m, 2H), 2.34 (dt, J=2.9 and 14.0 Hz), 2.42-2.49 (m, 1H), 2.77-2.86 (m, 1H), 4.71 (dd, 1H, J=1.7 and 4.7 Hz), 6.24 (d, 1H, J=5.7 Hz), 6.40 (dd, 1H, J=1.7 and 5.7 Hz); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 17.2, 22.0, 28.9, 37.2, 37.3, 50.0, 57.7, 8[illegible] 91.0, 135.8, 138.2, 209.4; Mass spectrum 192 (3, $M^+$), [illegible] (100, $M^+$-$CH_2$=C(OH)CH=CHCH$_3$ (retro IMDAF or McLafferty rearr.)); Analysis calc'd for $C_{12}H_{16}O_2$: C, 74.[illegible] H, 8.40. Found: C, 74.99; H, 8.16.

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(15) Interestingly, we have found that treatment of compound **12** with $CD_3Li$ in DME at r.t. provided **7b** with an ethyl group labeled as $CD_3CH_2$-. From the labeling and other studies, we believe that the ethyl compound **7b** is formed by methyllithium reacting with a methyl group of DME to form a "carbene" species", which immediately reacts with MeLi to form EtLi. The EtLi either attacks DME in the usual manner (β-hydride abstraction)[31] or reacts with the highly strained double bond of **12** providing **7b**. Details will be published at a later date.

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(17) Compound (±)-**13**: mp 105-106°C; IR (KBr) 3259 cm⁻¹; $^1$H-NMR (200 MHz, $CDCl_3$) δ 0.81, 0.85, 0.96 and [illegible] (three d, 3H each, J=7.0, 7.0, 6.0, and 6.2 Hz), 1.[illegible] (m, 1H), 1.43-1.82 (m, 6H), 2.06-2.19 (m, 2H), 2.[illegible] (m, 1H), 3.49 (dd, 1H, J=5.4 and 10.7 Hz), 5.45 (td, J=1.8, 1.8, and 6.2 Hz); $^{13}$C-NMR (50 MHz, CDC[illegible] 14.3, 14.4, 15.5, 22.5, 26.7, 30.1, 31.7, 35.2, 42.[illegible] 49.0, 75.0, 125.6, 136.2; Mass spectrum 208 (19, $M^+$), [illegible] (12, M-$H_2O$), 150 (100, retro Diels-Alder); Analysis

for $C_{14}H_{24}O$: C, 80.69; H, 11.63. Found: C, 80.39; H, 11.33.

(18) The stereochemistry of major isomer of compound **13** was proven as follows (Scheme 5). Treatment of the major isomer of 13 with TMSCl/NaI[32] in acetonitrile provided **18** in which the double bond had migrated. A Chatgilialoglu[19] modified Barton deoxygenation[20] of the alcohol provided **19** which has a $C_2$ axis of symmetry. The $^{13}C$ NMR spectrum of **19** contained only 8 lines and the $^1H$ NMR spectrum showed only two methyl doublets indicating the $C_{18}$ methyl group is as shown in **13**.

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(25) Compound (±)-**15**: bp 70-80°C/0.055 Torr; IR (neat) 2699, 1723, 1706 $cm^{-1}$; $^1H$-NMR (200 MHz, $CDCl_3$) δ 0.76, 0.83, 1.01, and 1.18 (four d, 3H each, J=7.2, 6.7, 6.0, and 7.0 Hz), 1.23-1.78 (m, 4H), 1.80-2.55 (m, 7H), 9.59 (d, 1H, J=1.9 Hz); $^{13}C$-NMR (50 MHz, $CDCl_3$) δ 13.1, 13.4, 15.1, 22.4, 26.3, 31.3, 33.9, 36.6, 41.9, 44.6, 51.8, 60.0, 205.3, 212.1; Mass spectrum 224 (2, $M^{+\cdot}$), 111 (100, M-$CH_2$=$CHCH_2CH(CH_3)CHO$-$CH_3$ (McLafferty rearr.-$CH_3$)); Exact mass calc'd for $C_{14}H_{24}O_2$: 224.1776. Found: 224.1779.

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(30) Compound (±)-**8**: bp 140-150°C/0.08 Torr; IR (neat) 3377, 1461, 1425 $cm^{-1}$; $^1H$-NMR (400 MHz, $CDCl_3$) δ 0.85, 0.86, 0.88, and 0.89 (four overlapping d, 12H, J=6.6, 6.6, 6.6, and 6.5 Hz), 1.07 (s, 9H), 1.10-1.77 (m, 12H), 3.08 (br s, 1H, $H_6$), 3.48 (d, 2H, J=6.4 Hz), 3.65-3.73 (br m, 2H), 7.36-7.45 and 7.66-7.68 (m, 6H and 4H); $^{13}C$-NMR (100 MHz, $CDCl_3$) δ 12.8, 2 x 16.2, 2 x 19.3, 26.7, 3 x 26.9 (*t*-Bu), 32.2, 33.2, 33.3, 35.4, 40.8, 41.8, 61.1, 70.1, 80.6, 4 x 127.6, 2 x 129.5, 4 x 135.6, 2 x 134.1; Mass spectrum: (no $M^{+\cdot}$), 409 (1, M-$H_2O$-*t*-Bu), 391 (2, M-2$H_2O$-*t*-Bu), 199 (100, $Ph_2SiOH^+$); Exact mass calc'd for $C_{26}H_{37}O_2Si$ (M-$H_2O$-*t*-Bu): 409.2563. Found: 409.2554.

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