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VIRGINIAMYCIN M: ABSOLUTE CONFIGURATION AND SYNTHETIC STUDIES

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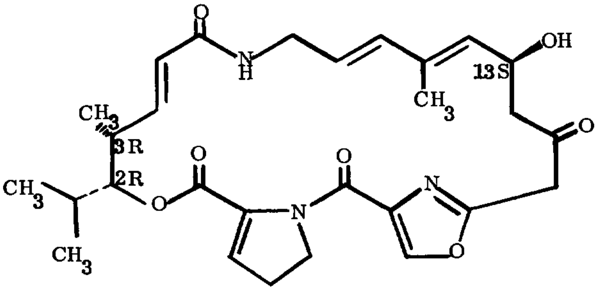
Summary: Correlation studies during total synthesis have unambiguously established the 2R, 3R, 13S absolute configuration of virginiamycin M.

Virginiamycin M 1 (designated VM; also known *inter alia* as ostreogrycin A, mikamycin A and staphylomycin A) is one of a complex of synergistic antibiotics found in *S. virginiae* which are individually bacteriostatic but bacteriocidal as a mixture.[2] In procaryotic cell free systems, reversibly bound VM inhibits aminoacyl-tRNA linkup to the ribosomal A-site and causes lasting damage to the organism's protein synthesizing apparatus. Since the classical structural elucidation of VM in 1966,[3] this polyheterocyclic macrocycle has been the object of both crystallographic[4] and biosynthetic[5] investigations. Nevertheless its absolute configuration has yet to be established conclusively.[6] We have of necessity addressed this question in planning an enantioselective total synthesis of VM, and now report the correlation of a chiral synthetic intermediate (+)13 with (+)16, a key degradation product of VM. These experiments confirm that the tentative[6] 2R, 3R, 13S configurational assignment shown in 1 is indeed correct.

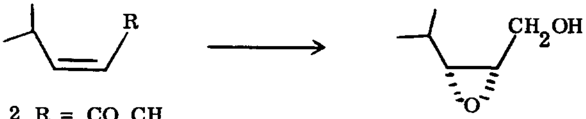


1

Reduction of *cis*-enoate 2[7] with diisobutylaluminum hydride furnished alcohol 3 [bp 59-61° (16 Torr)].[8] Chiral epoxidation of 3 using (+) diethyl tartrate-titanium (IV) isopropoxide-*t*-BuOOH according to Sharpless[9] afforded (2S, 3R)-epoxyol 4 $[\alpha]_D$=-9.9° (c 2.75, $CHCl_3$) in 54% yield. The empirical guidelines proposed for this process[8,10] suggested that our product had the absolute configuration designated in the Scheme. To determine the extent of asymmetric induction, 4 was alkylated with $Li(CH_3)_2Cu$ (5 equiv, ether, -20→0°). This regiospecific epoxide opening[11] generated a single diol 5 [87% after flash chromatography; 47% after recrystallization; mp 84-85°; $[\alpha]_D$ = -164° (c 0.64, $CHCl_3$); NMR δ (300 MHz, $CDCl_3$) 3.73, 3.72 (ABX, 2H, $-CH_2O-$, J_{gem}=10.9 Hz, J_{vic}=4.2, 5.2 Hz), 3.42 (dd, 1H, -CHO-, J=2.2, 8.4 Hz), 1.85 (m, 1H), 1.70 (m, 1H), 0.99, 0.95, 0.85 (3d, 9H, J=7 Hz); CIMS (methane) m/z 133 (M+1, 88%), 115 (M+1 $-H_2O$, base)]. Stepwise acylation of 5 with PhCOCl (98%), then with (-) methoxytrifluoromethylphenylacetic acid according to Mosher[12] gave 7 whose analysis by ^{19}F-NMR indicated a 66% enantiomeric excess in structures 5 and 6.

Quantitative protection of benzoate 6, $[\alpha]_D$ = -3.75° (c 0.83, $CHCl_3$), as its THP ether 8 followed by saponification afforded 9 (100%) as a pair of diastereomers. Before attaching carbons 5 and 6 corresponding to VM, the absolute chirality at carbons 2 and 3 of 9 was conclusively established by its oxidation to (-)10 (PDC-DMF,[13] then CH_2N_2) whose configuration was independently established.[14] This outcome validated our initial assignment of chirality to 4 using the Sharpless mnemonic.

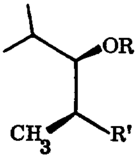
Controlled Collins oxidation of 9 in CH_2Cl_2[15] furnished aldehyde(s) 11 [89%; NMR δ 9.80, 9.70 (two s, diastereomeric -CHO)] whose condensation with triethyl phosphonoacetate (*n*BuLi, THF, rt, 1h) produced *trans*-enoate(s) 12 in 65% yield. Removal of the THP ether using pyridinium tosylate (EtOH, 60°, 92%) led to the key heptenoic ester 13 $[\alpha]_D$= +15.8° (c, 1.15, $CHCl_3$) for VM total synthesis [NMR δ 6.91 (ddd, H_3, $J_{2,3}$ = 16 Hz, $J_{3,4}$=8 Hz), 5.85 (dd, H_2, $J_{2,4}$= 1.1 Hz); IR λ_{max} (film) 5.85, 6.05 μ].



<u>2</u> R = CO_2CH_3

<u>3</u> R = CH_2OH

<u>4</u>



<u>5</u> R =H, R' = CH_2OH

<u>6</u> R =H, R' =CH_2OCOPh

<u>7</u> R =MTPA, R'=CH_2OCOPh

<u>8</u> R =THP, R'=CH_2OCOPh

<u>9</u> R =THP, R'=CH_2OH

<u>10</u> R =H, R'=CO_2CH_3

<u>11</u> R =THP, R'=CHO

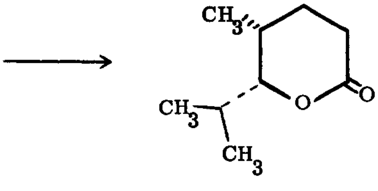
<u>12</u> R =THP, R'=t-CH=$CHCO_2Et$

<u>13</u> R =H, R'=t-CH=$CHCO_2Et$

<u>14</u> R =H, R'=$CH_2CH_2CO_2Et$

<u>15</u> R =H, R'=$CH_2CH_2CO_2H$

<u>15</u>



<u>16</u>

It was an easy matter to transform (+)<u>13</u> into the virginiamycin-derived lactone <u>16</u> by reduction (H_2/Pd/C, 93%), saponification (KOH-CH_3OH) and acid-catalyzed cyclization of hydroxyacid <u>15</u> (p-TsOH-C_6H_6, reflux; 83% from <u>14</u>). Synthetic <u>16</u> exhibited spectral data fully in accord with that published for the naturally occurring material. Moreover the specific rotation of synthetic <u>16</u> (+56°), when corrected for the extent of asymmetric epoxidation (+85°) was in good agreement with the reported value[3] of +96°. Further elaboration of (+)<u>13</u> into <u>1</u> is in progress.

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