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Total Synthesis of Myxovirescin A_1

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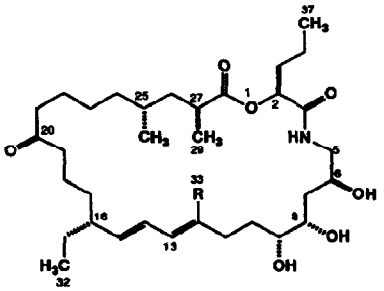
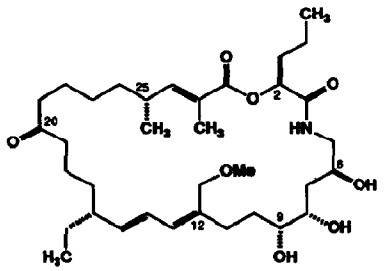
Abstract: *Stereocontrolled synthesis of myxovirescin A_1 (1a), a 28-membered macrolactam lactone, is accomplished via a highly convergent route. Ring closure of the macrocycle is realized by macrolactamization using the Mukaiyama procedure.*

The myxovirescins, consisting of thirty-one macrolactam lactone antibiotics, were first isolated from the fermentation broth of *Myxococcus virescin* (Mx v 48).[1] A predominant component, myxovirescin A_1, inhibits the growth of *E. coli* and other enterobacteria.[2] The structure elucidation of myxovirescin A_1 (1a) was accomplished by X-ray crystallography of the bisacetonide of 1a in conjunction with degradation experiments.[1,3] We have previously reported total synthesis of myxovirescin B (1c), demonstrating ring closure via the intramolecular Horner-Emmons reaction.[4] Myxovirescin M_2 (1b) was synthesized by Seebach and coworkers,[5] using a Yamaguchi macrolactonization. Herein, we report the total synthesis of myxovirescin A_1, establishing construction of the *anti*-1,3-dimethyl substitution pattern for C_{25}-C_{27} and a new strategy for ring closure affording these antibiotics via macrolactamization.



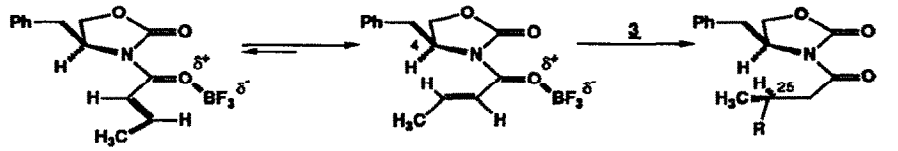
Myxovirescin A_1 (1a) R = CH_2OMe
Myxovirescin M_2 (1b) R = CH_3



Myxovirescin B (1c)

Our initial efforts to selectively produce the 25(*R*), 27(*R*)-dimethyl substitution of Myxovirescin A_1 via conjugate hydride reductions of 1c and its protected derivatives were not satisfactory. This led us to redesign our synthesis strategy to accommodate introduction of the 1,3-*anti*-dimethyl substituents of 1a as illustrated in Scheme I. Conjugate addition to the 4(*S*)-benzyl-2-oxazolidinone 2[6] occurred with high diastereofacial selectivity using the organocopper-boron trifluoride procedure developed by Yamamoto.[7] Thus, 3-benzyloxy-2(*R*)-methyl-1-bromopropane was converted to its corresponding Grignard reagent (Mg°, THF, reflux) followed by addition of purified cuprous iodide (1 equiv. at -30 °C, 0.5 hr) with subsequent cooling to -78 °C and dropwise introduction of freshly distilled BF_3•Et_2O (1.0 equiv.). The organocopper species 3 afforded oxazolidinone 4 in nearly quantitative yield (96%) as a 9:1 ratio of C-25 isomers. Other preparations for mixed Gilman reagents or cuprates, derived from our starting bromide, gave reduced yields and problematic mixtures of diastereomers.

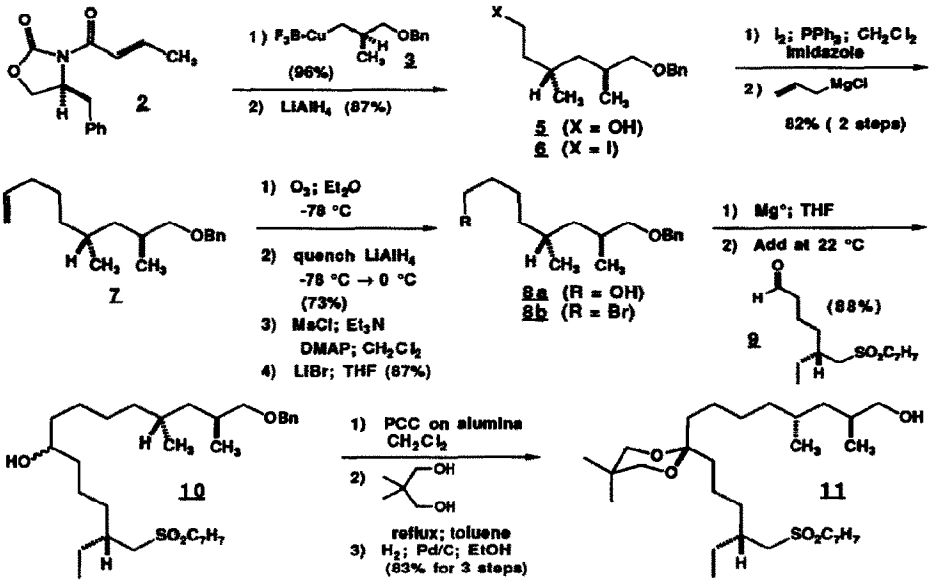
The diastereoselection of our conjugate addition is rationalized by Lewis acid coordination to provide, for steric reasons, an enhanced preference for the *s*-trans conformer 2b. Proximity to the C-4 chiral center of 2b effects nucleophilic addition to the less hindered, re-face of the unsaturated system.



2a (*s-cis*) 2b (*s-trans*) 4 (R = $CH_2CH(CH_3)CH_2OBn$)

Our results feature the same general outcome of cuprate additions as reported for the camphor-based auxiliaries of unsaturated esters described by Oppolzer,[8] and the unsaturated imides of Koga.[9,10] However, additional studies have demonstrated that stereoselectivity may also be highly dependent upon the nature of the cuprate reagent.[11]

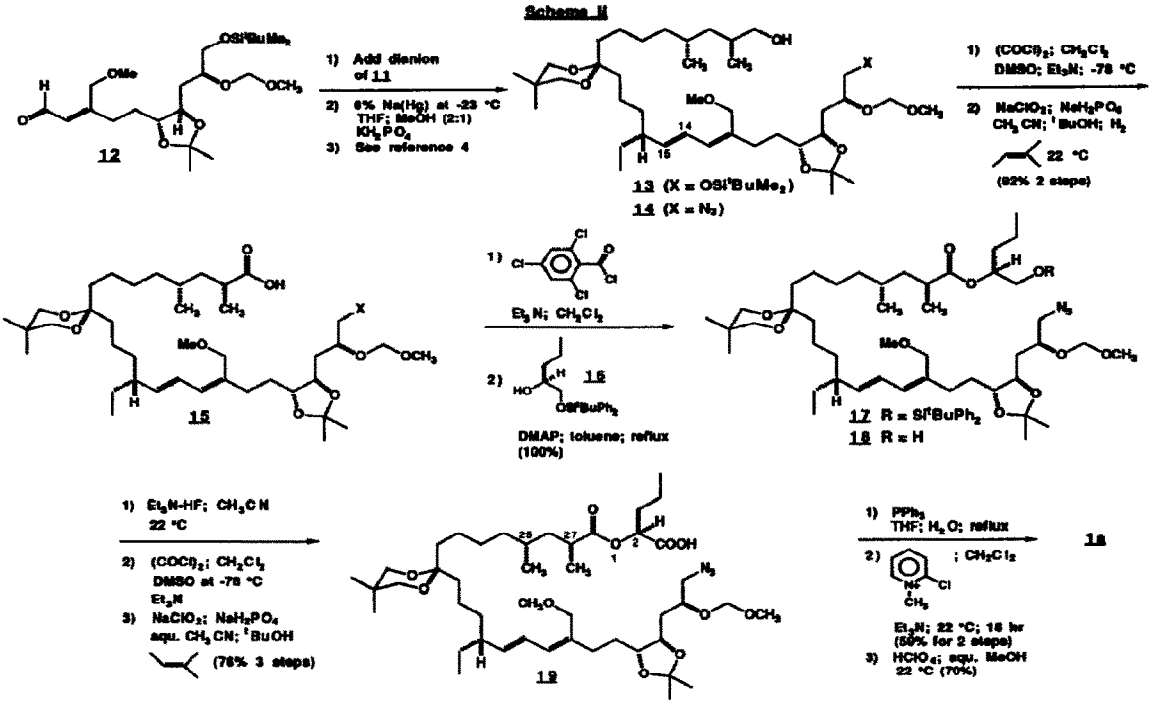
Scheme I



Alcohol 5 (Scheme I) was produced upon hydride reduction of 4. Conversion to the iodide 6 was followed by coupling with allylmagnesium chloride to yield alkene 7. Standard techniques led to the primary bromide 8b, which was transformed to its Grignard reagent for addition to the aldehydic sulfone 9.[4,12] The resulting mixture of alcohols 10 underwent oxidation, ketalization and deprotection to produce optically pure sulfone 11 in 83% overall yield from 10.

Following the precedence established in our myxovirescin B synthesis, the Julia-Lythgoe reductive coupling of components 11 and 12 proceeded smoothly (Scheme II) without the usual acylation of the intermediate β-sulfonyl alcohols prior to treatment with sodium-amalgum. The crude product 13 was obtained in 69% overall yield as a mixture of *E*/*Z* C_{14}-C_{15} isomers (ratio 6.5:1), with transformation to the azide 14 as previously described.[4]

Our route to myxovirescin A_1 necessitated a new strategy for macrocyclization. These results are summarized in Scheme II. Oxidation of the primary alcohol at C_{28} to the carboxylic acid 15 without epimerization or deprotection was crucial. This was accomplished in a mild two-step sequence employing a Swern reaction followed by a buffered sodium chlorite oxidation of the intermediate aldehyde.[13]



In situ, 2-methyl-2-butene served as a scavenger for electrophilic byproducts sparing the diene moiety of 15 from allylic oxidation. Esterification of 15 with 2(*S*)-1-*tert*-butyldiphenylsiloxy-2-pentanol (16)[14] using the Yamaguchi protocol[15] provided ester 17 in quantitative yield. Desilylation of 17 with *n*-$Bu_4N^+F^-$ in THF afforded a 1:1 ratio of primary alcohol 18 and isomeric secondary alcohol resulting from intramolecular acyl transfer. This rearrangement was minimized to 10% or less using HF•Et_3N in acetonitrile for the deprotection of 17. Sequential oxidations of 18, as previously described for alcohol 14, gave the carboxylic acid 19 (76% overall yield) without α-epimerizations. Our efforts to incorporate 2(*S*)-hydroxypentanoate derivatives for esterifications of 15, leading directly to 19, produced substantial isomerization at C_2 and at C_{27} as well as problems for selective hydrolysis and deprotection of esters of 19.

Finally macrolactamization was accomplished via the quantitative reduction of 19 to the corresponding amino acid with triphenylphosphine in aqueous THF at reflux. Purification by silica gel chromatography and subsequent cyclization utilizing Mukaiyama conditions[16] for acyl activation afforded the twenty-eight membered macrocycle in 59% yield from 19. Acid-promoted deprotection was achieved upon stirring in aqueous methanol yielding synthetic myxovirescin A_1 ($[\alpha]_D^{24}$ +26.8° (MeOH, C = 0.38)) which was identical in all respects to a sample of natural product generously supplied by Trowitzsch-Kienast.[17]

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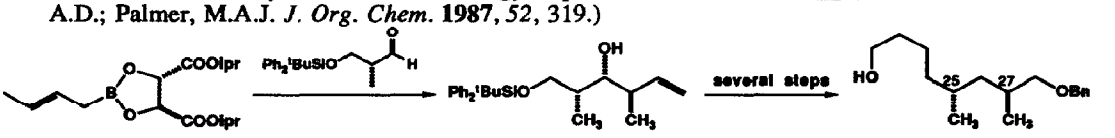
12. To confirm our stereoassignments, alcohol 8a was also prepared in a multistep sequence utilizing the tartrate-based *E*-crotylboronate methodology to provide known alcohol 8c (Roush, W.R.; Palkowitz, A.D.; Palmer, M.A.J. *J. Org. Chem.* **1987**, *52*, 319.)



8c 8a $[\alpha]_D^{24}$ -9.6° (c = 2.4, $CHCl_3$)

Small amounts (5-10%) of the C-25 diastereomer of 8a were conveniently removed, on a preparative scale, following column chromatography of diene 13.

13. For a recent procedure: Lubell, W.D.; Jamison, T.F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511.
14. Alcohol 16 was produced by reduction of 2(*S*)-hydroxypentanoic acid with $LiAlH_4$ in ether yielding a diol, which was selectively protected with *tert*-butyldiphenylsilyl chloride.
15. For a literature procedure: Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221.
16. For an example of macrolactamization: Jones, T.K.; Reamer, R.A.; Desmond, R.; Mills, S.G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. After macrolactamization, the C_{26}-C_{27} olefin isomers were easily separated by flash chromatography.
17. All synthetic compounds were purified and fully characterized. We thank Dr. Wolfram Trowitzsch-Kienast, Gesellschaft für Biotechnology Forschung, Mascheroder Weg 1, D-3000, Braunschweig, Germany, for a pure sample of Myxovirescin A_1.

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