198. A Highly Convergent Total Synthesis of (+)-Myxovirescine M_2

Preliminary Communication

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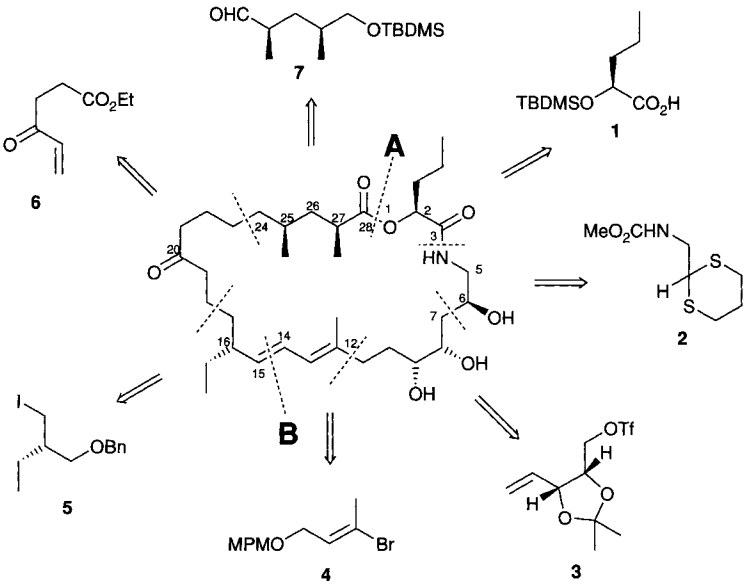
The antibiotic myxovirescine M_2 was synthesized from seven building blocks (**1–7**, *Scheme 1*), with the following chiral starting materials being employed: (*S*)-malic acid, (+)-D-ribonolactone, (*S*)-2-(hydroxymethyl)butanoate , and (2*R*,4*S*)-5-hydroxy-2,4-dimethylpentanoate. Three new nucleophilic reagents, **8–10**, for C–C bond formation have been used. The key steps of the synthesis are: a *Suzuki* coupling between an alkyl borane and a vinyl bromide (**4** + **12e** → **13**), a *Julia* olefination (**14** + **17** → **18**), and a *Yamaguchi* macrolactonization to form the 28-membered lactone (**18** → **19**). This extremely convergent synthetic approach will allow the preparation of a number of the 31 known myxovirescine molecules.

The myxovirescines [1] are ideal target molecules for EPC syntheses using the building-block approach [2], because all but one of their stereogenic centers are separated by at least one non-stereogenic center. They contain nine or ten stereogenic units alltogether. We chose myxovirescine M_2 (*Scheme 1*), since it is one of the most active antibiotics in the series, and since the building blocks could be chosen such that other members of the family (A_2, F_1, I_1, L, and S [1]) will be available by minor modifications of the starting fragments. So far, only myxovirescine B has been the object of a synthetic effort using different key steps and starting materials [3].

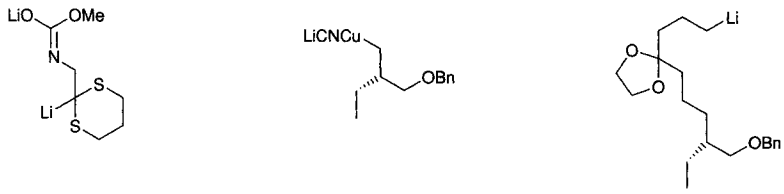
The key fragments employed are shown in *Scheme 1*: the chirality center of the protected hydroxy-acid **1** is derived from (*S*)-malic acid, the dithiane **2** from commercially available aminoacetaldehyde acetal, the triflate **3** from ribonolactone, the vinyl bromide **4** from crotyl alcohol, the iodo-ether **5** from ethyl butanoate, the unsaturated keto-ester **6** from methyl vinyl ketone, and the aldehyde **7** from *meso*-dimethylglutaric acid.

Scheme 1



Bn = $PhCH_2$, MPM = 4-MeO–$PhCH_2$, TBDMS = (*t*-Bu)Me_2Si, Tf = CF_3SO_2

The immediate precursors to the macrocyclic ring are the fragments O(1) – C(14) and C(15) – C(28) which are connected with formation of the bonds indicated by A and B. For the five C–C coupling steps, we have used the three new nucleophilic organometallic reagents **8**, **9**, and **10**, a *Julia* [4] and a *Suzuki* [5] reaction; the final cyclization is achieved by a *Yamaguchi* lactonization [6].

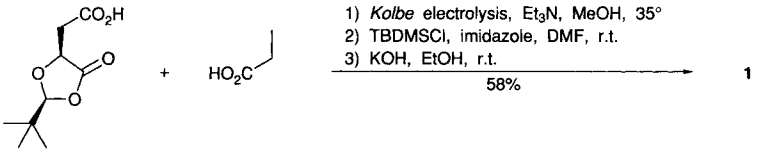


8 **9** **10**

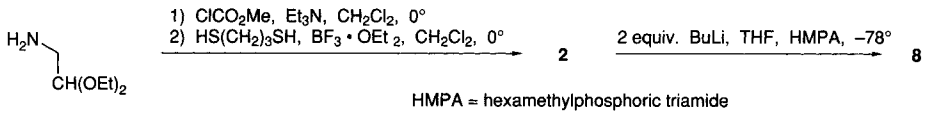
The fragment preparation is outlined in *Schemes 2–5*, and their assembly in *Schemes 6–8*. Following a procedure developed by us [7], the dioxolanone from (*S*)-malic acid and pivalaldehyde is subjected to a *Kolbe* cross-coupling electrolysis with propionic acid, affording directly the methyl ester of hydroxypentanoic acid under the conditions employed. Protection of the OH group and saponification give the acid **1** (*Scheme 2*). Methoxycarbonylation and transacetalization in the usual way [8] convert 2-aminoacetaldehyde

diethyl acetal to the dithiane **2** which can be metallated to the dilithium derivative **8** (*Scheme 3*). The yeast-reduction product of ethyl 2-formylbutanoate (easily prepared from ethyl butanoate) [9] is converted to the iodide **5** by benzyl-ether formation, ester reduction, and nucleophilic substitution of the primary OH group by iodide; I/Li exchange with 2 equiv. of *t*-BuLi [10] and addition of CuCN lead to the cuprate **9** (*Scheme 4*). There are various methods of going from *meso*-2,4-dimethylglutarate to enantiomerically pure derivatives [11]; we chose to use the resolution of the half-ester through diastereoisomeric phenethylammonium salts [11e,g] and borane reduction to the enantiomeric hydroxy-esters **11** which are *both* converted to the desired aldehyde **7**; see the sequence of reactions given in *Scheme 5*.

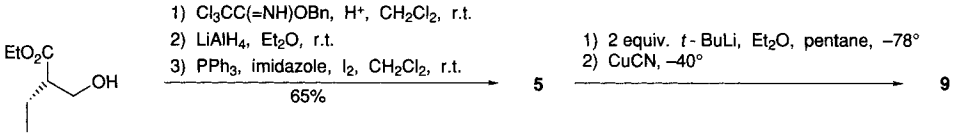
Scheme 2



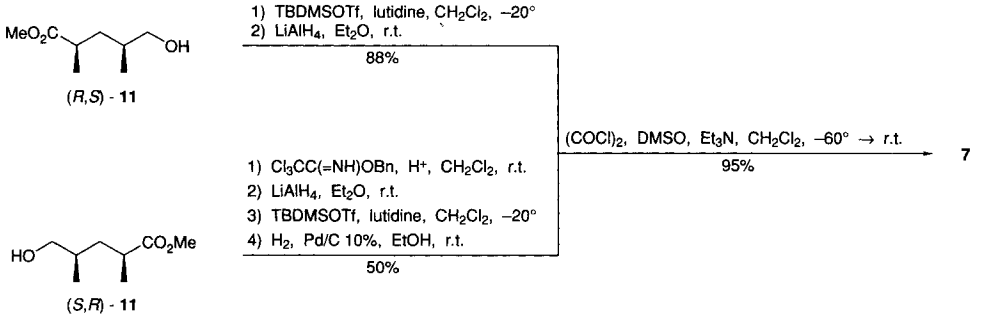
Scheme 3



Scheme 4

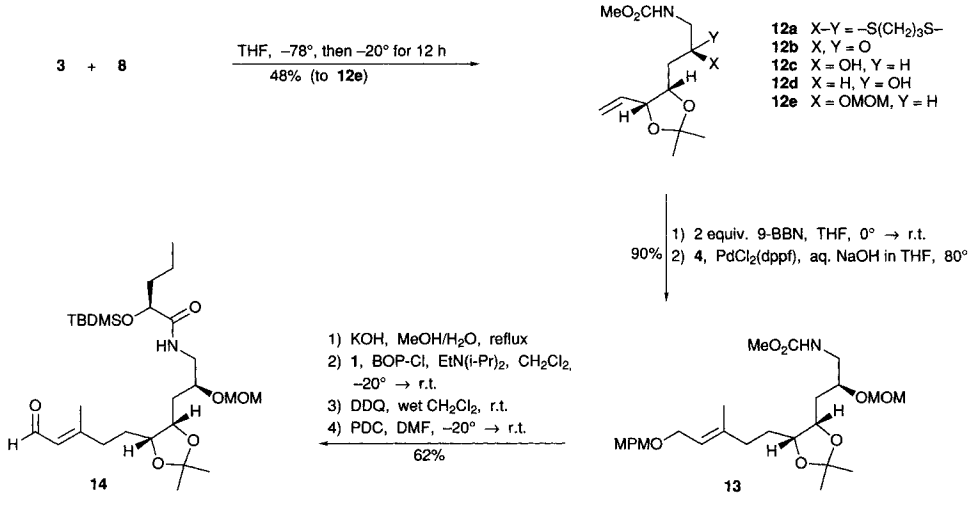


Scheme 5



The construction of the two key units **14** and **17** is presented in *Schemes 6* and *7*. First, we alkylate the dilithio compound **8** with the triflate **3** obtained from *cis*-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-methanol [12] under standard conditions [13] (→ **12a**). NCS-Mediated dithiane hydrolysis [8], reduction of the oxo group ($LiAlH(t\text{-}BuO)_3$) to a 1:1 mixture of the alcohols **12c** and **12d** (separation by chromatography and assignment of configuration by ^{1}H-NMR spectroscopy), *Mitsunobu* inversion [14] of **12d**, and protection of the OH group gives the N(4) – C(11) building block **12e**. Then, we form the C(11)–C(12) bond by Pd-catalyzed coupling [5] of the borane from **12e** and 9-BBN with the 4-methoxybenzyl-protected bromo-allylic alcohol **4** [15] to give **13**. The assembly of the south-eastern part O(1) – C(14) **14** is completed by carbamate cleavage, followed by amide formation with the acid **1** using the BOP-active ester method [16], debenzylation, and oxidization to the α,β-unsaturated aldehyde (*Scheme 6*).

Scheme 6

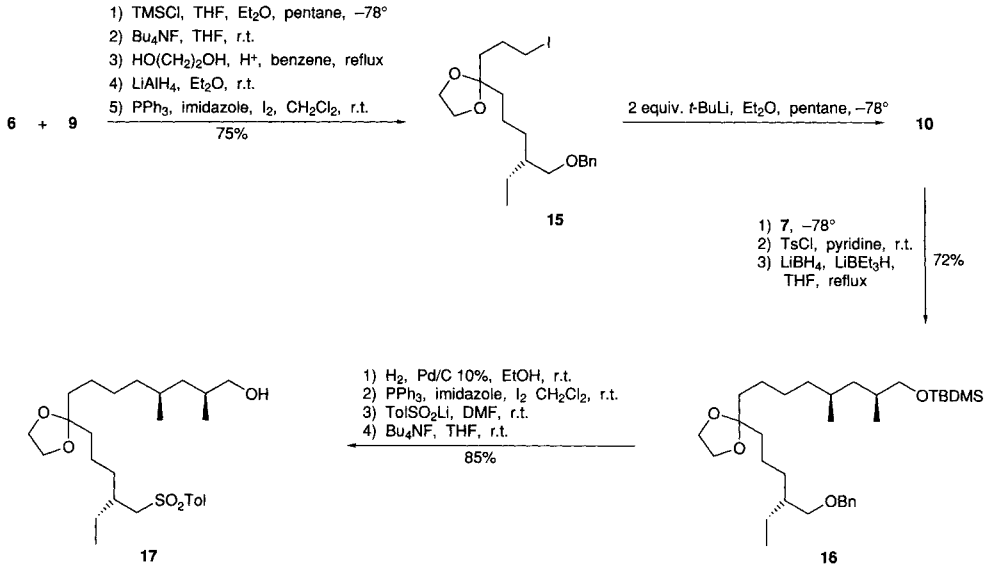


dppf = 1,1'-bis(diphenylphosphino)ferrocene, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, MOM = methoxymethyl, PDC = pyridinium dichromate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

The synthesis of the north-western portion C(15) – C(28) **17** is outlined in *Scheme 7* and consists of *Michael* addition of the cuprate **9** to the enone **6** [17]; oxo-group protection, ester reduction and conversion to the iodide **15** (conditions as for **5**), metallation (→ **10**), addition to the aldehyde group of **7**, and deoxygenation through the tosylate provide the unsymmetrically protected dihydroxy-ketal **16**. Conversion of **16** to hydroxy-sulfone **17**, to be employed in the *Julia* coupling, was then accomplished by debenzylation, OH/I exchange, *p*-tolylsulfone formation, and desilylation.

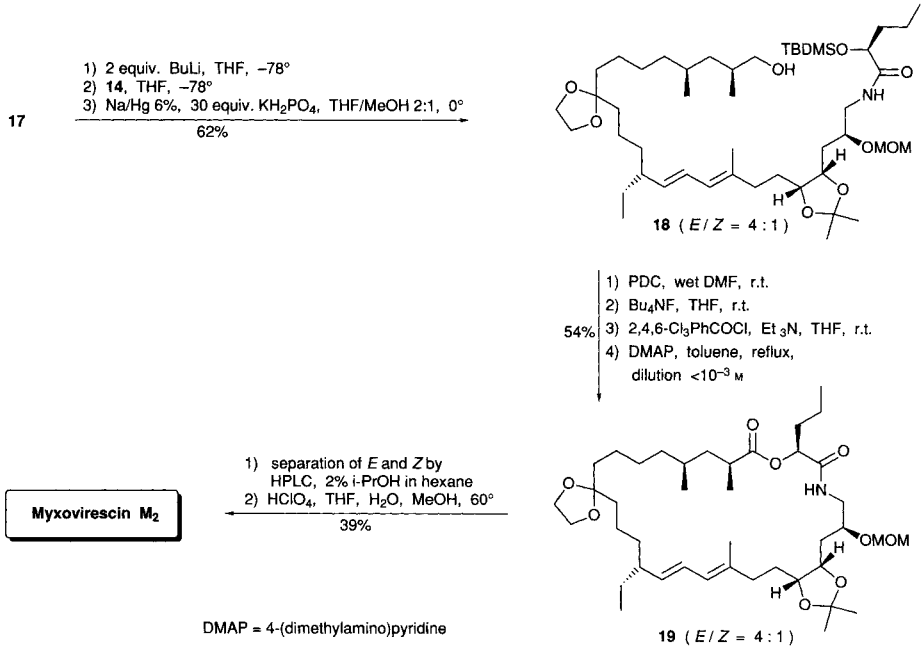
The two large fragments are joined by addition of the dilithiated hydroxy-sulfone **17** to the α,β-unsaturated aldehyde **14** and reductive elimination with Na/Hg [3][4] to a 4:1 mixture of the (*E*/*Z*)-isomers of **18** (*Scheme 8*). Finally, the stage was set for the

Scheme 7



TMS = Me_3Si, Tol = 4-Me-Ph

Scheme 8



DMAP = 4-(dimethylamino)pyridine

macrocyclization by oxidation of the primary alcohol group to the corresponding acid and silyl-ether cleavage. Our previous good experience [11a][18] with the *Yamaguchi* conditions [6] for this kind of ring closure made us wager 38 mg of the hydroxy-acid, *i.e.* half of the total amount of material available at this stage. We were rewarded by isolation of 83% of the lactones **19** which could be separated by preparative HPLC to give the major, desired diastereoisomer (17 mg, 46% yield). Deprotection under acidic conditions [3], *i.e.* cleavage of all the acetal-type moieties, produces the target molecule which is shown to be myxovirescine M_2 by comparison of its (+)-sign of specific rotation and of its ^{1}H- (*Fig.*) and ^{13}C-NMR spectra with those reported in [1b].

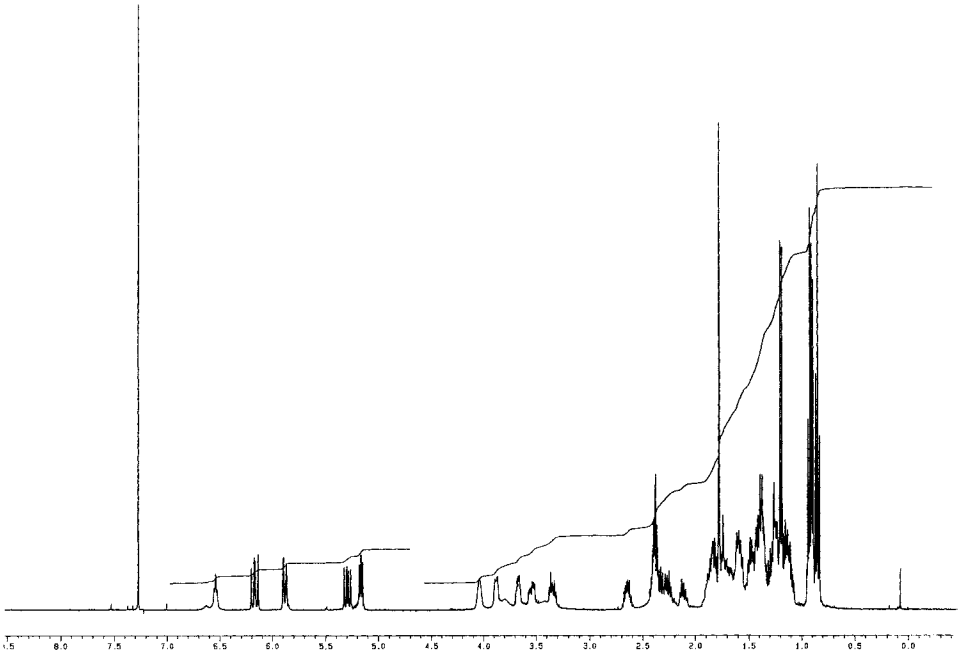


Figure. *400-MHz ^{1}H-NMR Spectrum of myxovirescine M_2 obtained by total synthesis*

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REFERENCES

[1] a) W. Trowitzsch-Kienast, V. Wray, K. Gerth, D. Schomburg, G. Höfle, *Liebigs Ann. Chem.* **1985**, 1629; b) W. Trowitzsch-Kienast, K. Schober, V. Wray, K. Gerth, H. Reichenbach, G. Höfle, *ibid.* **1989**, 345.

[2] D. Seebach, H.-O. Kalinowski, *Nachr. Chem. Techn. Lab.* **1976**, *24*, 415.

[3] D. R. Williams, J. M. McGill, *J. Org. Chem.* **1990**, *55*, 3457.

[4] D. V. Patel, F. VanMiddlesworth, J. Donaubauer, P. Gannett, C. J. Sih, *J. Am. Chem. Soc.* **1986**, *108*, 4603; P. J. Kocienski, *Chem. Ind. (London)* **1981**, 548; M. Julia, J. M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833.

[5] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314.

[6] J. Mulzer, H. M. Kirstein, J. Buschmann, C. Lehmann, P. Luger, *J. Am. Chem. Soc.* **1991**, *113*, 910; M. Yamaguchi, J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[7] D. Seebach, P. Renaud, *Helv. Chim. Acta* **1985**, *68*, 2342.

[8] B.-T. Gröbel, D. Seebach, *Synthesis* **1977**, 357; D. Seebach, *ibid.* **1969**, 17.

[9] J. Ehrler, F. Giovannini, B. Lamatsch, D. Seebach, *Chimia* **1986**, *40*, 172.

[10] a) W. F. Bailey, E. R. Punzalan, *J. Org. Chem.* **1990**, *55*, 5404; D. Seebach, H. Neumann, *Chem. Ber.* **1974**, *107*, 847; b) E. J. Corey, N. W. Baez, *Tetrahedron Lett.* **1985**, *26*, 6019; J. P. Gorlier, L. Hamon, J. Levisalles, J. Wagnon, *J. Chem. Soc., Chem. Commun.* **1973**, 88.

[11] a) C. Schregenberger, D. Seebach, *Liebigs Ann. Chem.* **1986**, 2081; b) Y. Nagao, T. Inoue, K. Hashimoto, Y. Hagiwava, M. Ochiai, E. Fujita, *J. Chem. Soc., Chem. Commun.* **1985**, 1419; c) Y.-F. Wang, C.-S. Chen, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1984**, *106*, 3695; d) P. Mohr, N. Waespe-Sarcevic, C. Tamm, K. Gawronska, J. K. Gawronski, *Helv. Chim. Acta* **1983**, *66*, 2501; e) R. W. Hoffmann, H. J. Zeiß, W, Ladner, S. Tabche, *Chem. Ber.* **1982**, *115*, 2357; f) C.-S. Chen, Y. Fujimoto, C. J. Sih, *J. Am. Chem. Soc.* **1981**, *103*, 3580; g) S. Masamune S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem.* **1980**, *92*, 573.

[12] V. Jäger, B. Häfele, *Synthesis* **1987**, 801.

[13] P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85.

[14] O. Mitsunobu, *Synthesis* **1981**, 1.

[15] E. J. Corey, M. G. Bock, A. P. Kozikowski, A. V. Rama Rao, D. Floyd, B. Lipshutz, *Tetrahedron Lett.* **1978**, *19*, 1051.

[16] R. D. Tung, M. K. Dhaon, D. H. Rich, *J. Org. Chem.* **1986**, *51*, 3351; J. Diago-Meseguer, A. L. Palomo-Coll, *Synthesis* **1980**, 547.

[17] E. Kunkel, I. Reichelt, H.-U. Reißig, *Liebigs Ann. Chem.* **1984**, 512; E. Kunkel, I. Reichelt, H.-U. Reißig, *Liebigs Ann. Chem.* **1984**, 802.

[18] D. Seebach, H.-F. Chow, R. F. W. Jackson, M. A. Sutter, S. Thraisrivongs, J. Zimmermann, *Liebigs Ann. Chem.* **1986**, 1281; D. Seebach, H.-F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thraisrivongs, J. Zimmermann, *J. Am. Chem. Soc.* **1985**, *107*, 5292; M. A. Sutter, D. Seebach, *Liebigs Ann. Chem.* **1983**, 939.