

198. A Highly Convergent Total Synthesis of (+)-Myxovirescine M₂

Preliminary Communication

by Dieter Seebach*, Miguel A. Maestro, Michael Sefkow, Axel Neidlein, Francine Sternfeld, Geo Adam,
and Thimo Sommerfeld

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum,
Universitätstrasse 16, CH-8092 Zürich

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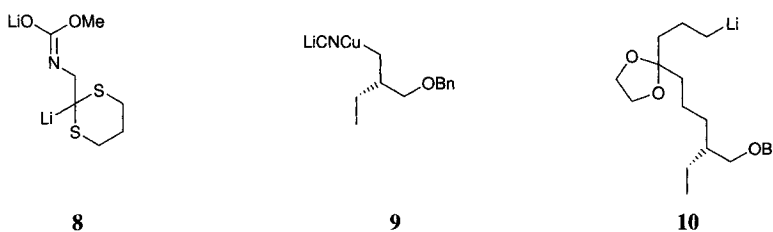
The antibiotic myxovirescine M₂ was synthesized from seven building blocks (**1–7**, *Scheme 1*), with the following chiral starting materials being employed: (*S*)-malic acid, (+)-D-ribonolactone, (*S*)-2-(hydroxymethyl)butanoate, and (2*R*,4*S*)-5-hydroxy-2,4-dimethylpentanoate. Three new nucleophilic 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 altogether. We chose myxovirescine M₂ (*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 (A₂, F₁, I₁, 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.

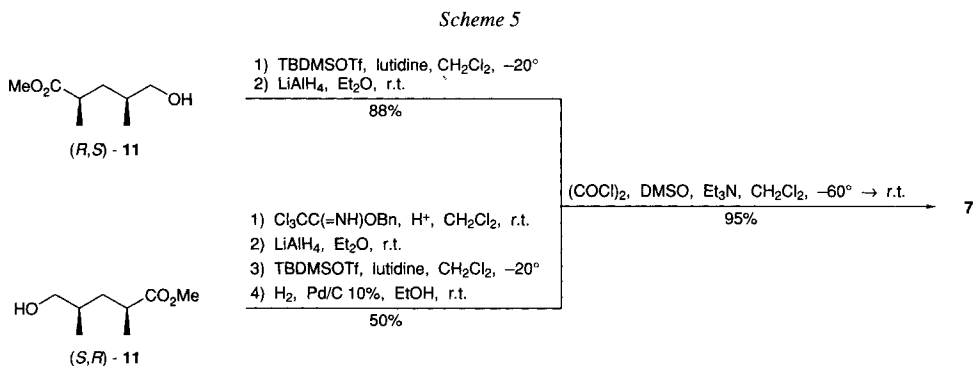
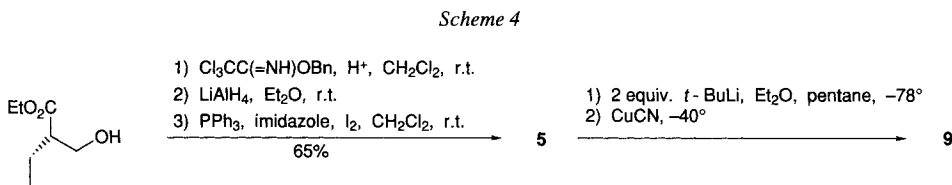
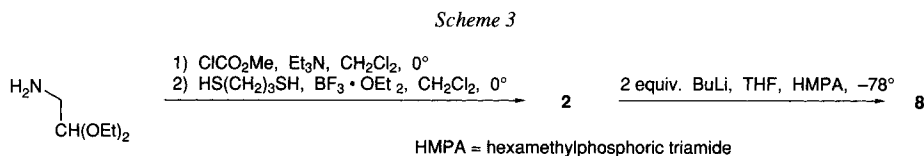
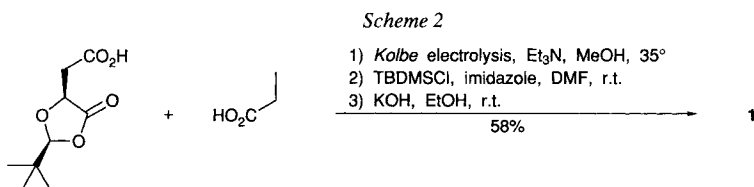
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The immediate precursors to the macrocyclic ring are the fragments O(1) – C(14) and C(15) – C(28) which are connected with formation of the bonds indicated by A and B. For the five C–C coupling steps, we have used the three new nucleophilic organometallic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



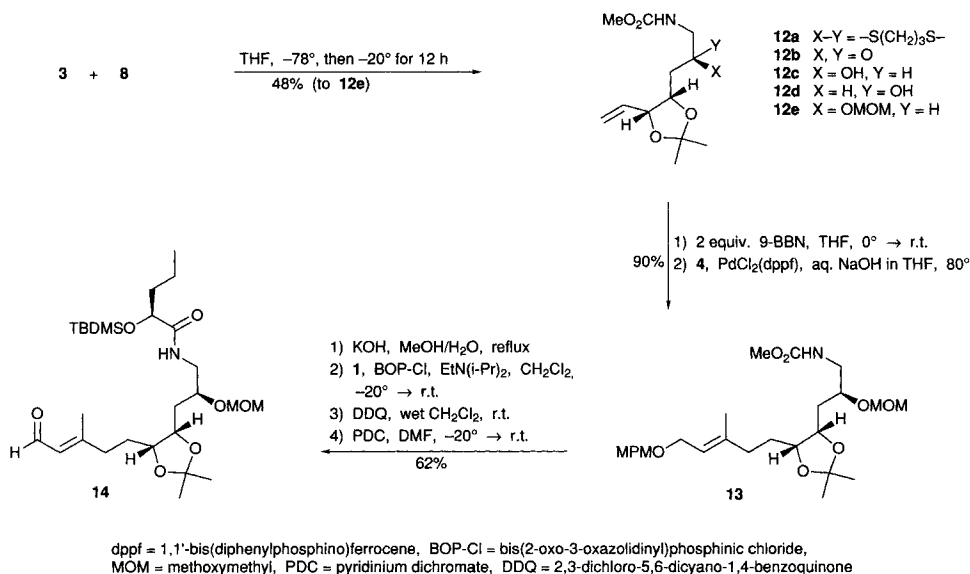
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diethyl acetal to the dithiane **2** which can be metallated to the dilithium derivative **8** (Scheme 3). The yeast-reduction product of ethyl 2-formylbutanoate (easily prepared from ethyl butanoate) [9] is converted to the iodide **5** by benzyl-ether 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.



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**] ($\rightarrow$ **12a**). NCS-Mediated dithiane hydrolysis [**8**], reduction of the oxo group ($\text{LiAlH}(t\text{-BuO})_3$) to a 1:1 mixture of the alcohols **12c** and **12d** (separation by chromatography and assignment of configuration by ^1H -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 oxidation to the α,β -unsaturated aldehyde (*Scheme 6*).

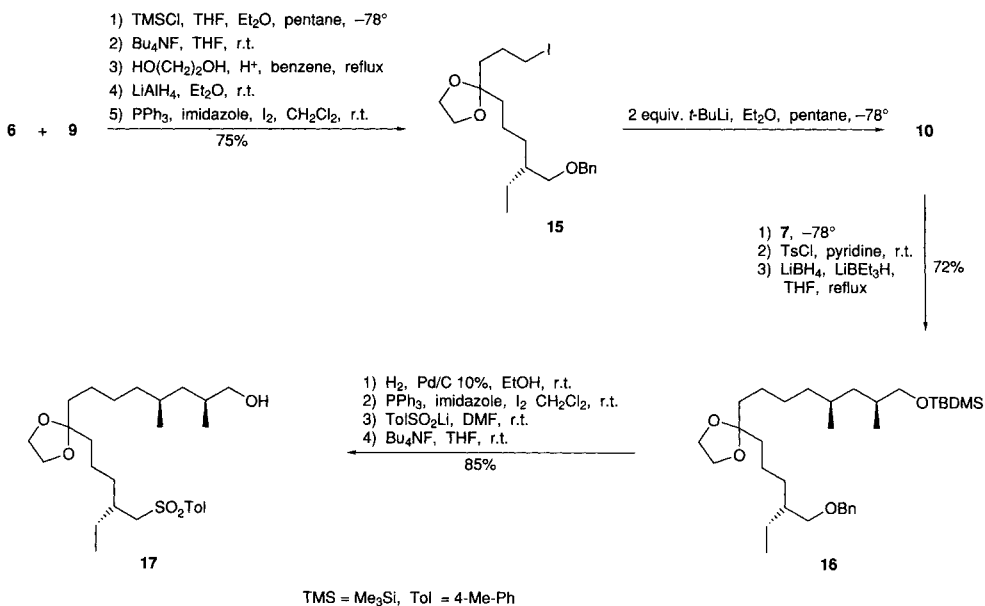
Scheme 6



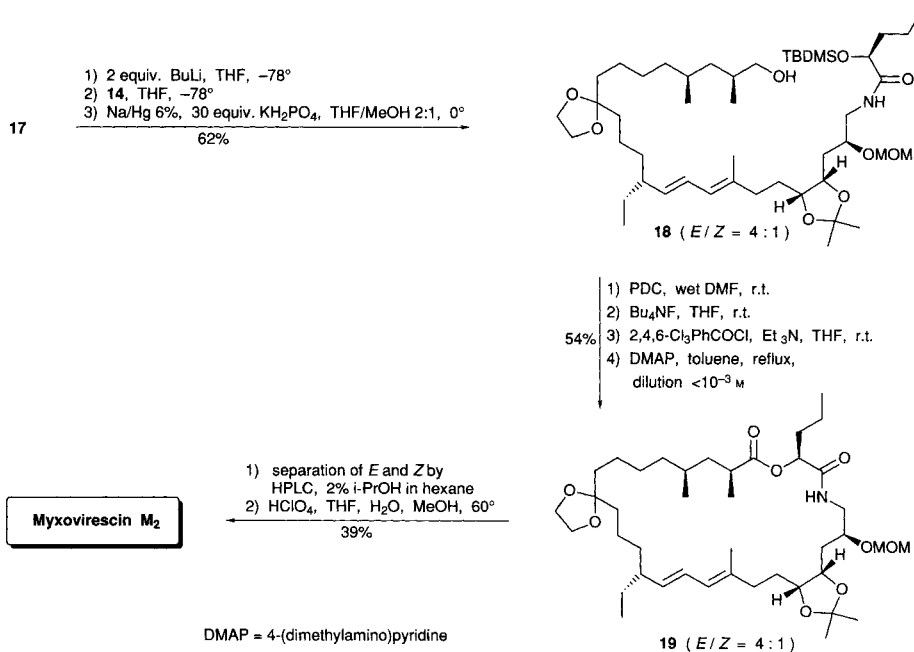
The synthesis of the north-western portion C(15) – C(28) **17** is outlined in *Scheme 7* and consists of *Michael* addition of the cuprate **9** to the enone **6** [**17**]; oxo-group protection, ester reduction and conversion to the iodide **15** (conditions as for **5**), metallation ($\rightarrow$ **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



Scheme 8



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 weigh 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 ^1H - (Fig.) and ^{13}C -NMR spectra with those reported in [1b].

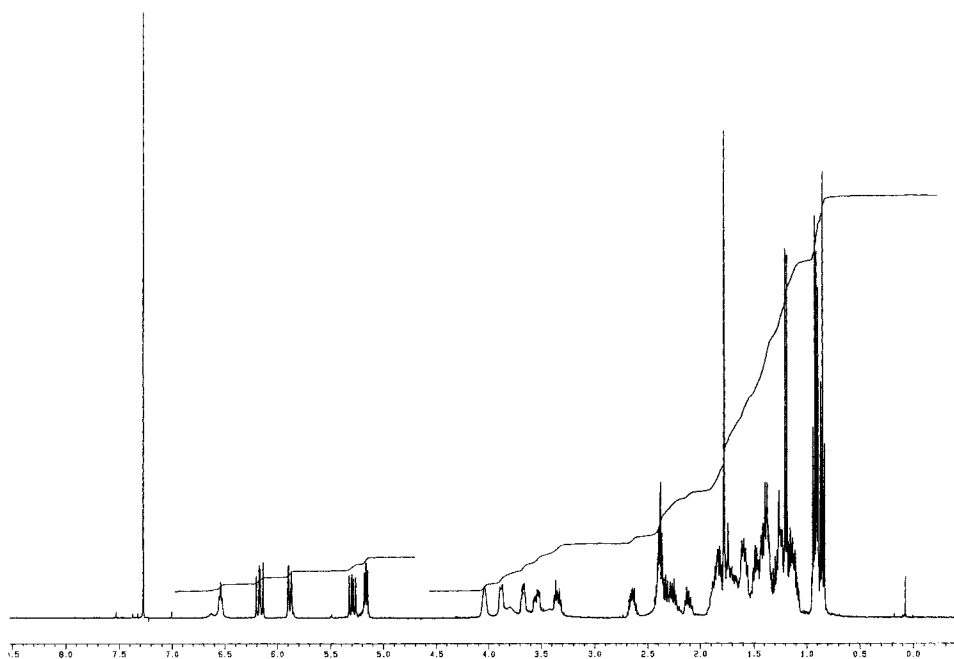


Figure. 400-MHz ^1H -NMR Spectrum of myxovirescine M_2 obtained by total synthesis

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