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

Preliminary Communication

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(31.X.91)

The antibiotic myxovirescine M₂ was synthesized from seven building blocks (1–7, Scheme I), with the following chiral starting materials being employed: (S)-malic acid, (+)-D-ribonolactone, (S)-2-(hydroxy-methyl)butanoate, and (2R,4S)-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 I), 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 I: 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.
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].

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). Methoxy-carbonylation 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 [11,e,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
1) Kolbe electrolysis, Et,N, MeOH, 35°
2) TBDMSOTf, imidazole, DMF, r.t.
3) KOH, EtOH, r.t. 58%

Scheme 3
1) ClCO2Me, Et3N, CH2Cl2, 0°
2) HS(CH2)3SH, BF3 * OEt2, CH2Cl2, 0°
3) KOH, EtOH, r.t.
HMPA = hexamethylphosphoric triamide

Scheme 4
1) Cl3CC(=NH)OBn, H+, CH2Cl2, r.t.
2) LiAlH4, Et2O, r.t.
3) PPh3, imidazole, l2, CH2Cl2, r.t. 65%
1) 2 equiv. t-BuLi, Et2O, pentane, -78°
2) CuCN, -40°

Scheme 5
1) TBDMSOTf, lutidine, CH2Cl2, -20°
2) LiAlH4, Et2O, r.t. 88%
1) Cl3CC(=NH)OBn, H+, CH2Cl2, r.t.
2) LiAlH4, Et2O, r.t.
3) TBDMSOTf, lutidine, CH2Cl2, -20°
4) H2, Pd/C 10%, EtOH, r.t. 95%
The construction of the two key units 14 and 17 is presented in Schemes 6 and 7. First, we alkylate the dilitio 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(γ-BuO)n) 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 oxidization 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 (→ 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

1) TMSCI, THF, Et2O, pentane, -78°
2) Bu4NF, THF, r.t.
3) HO(CH2)2OH, H+, benzene, reflux
4) LiAlH4, Et2O, r.t.
5) PPh3, imidazole, I2, CH2Cl2, r.t.

15

2 equiv. t-BuLi, Et2O, pentane, -78°

72%

1) TsCl, pyridine, r.t.
2) LiBH4, LiBEt3H, THF, reflux

TMS = Me3Si, Tol = 4-Me-Ph

Scheme 8

1) 2 equiv. BuLi, THF, -78°
2) 14, THF, -78°
3) NaHg 6%, 30 equiv. KH2PO4, THF/MeOH 2:1, 0°

62%

1) 2 equiv. BuLi, THF, -78°
2) 14, THF, -78°
3) PDC, wet DMF, r.t.
4) Bu4NF, THF, r.t.

54%

1) separation of E and Z by HPLC, 2% i-ProOH in hexane
2) HClO4, THF, H2O, MeOH, 60°

39%

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 M₂ by comparison of its (+)-sign of specific rotation and of its ¹H- (Fig.) and ¹³C-NMR spectra with those reported in [1b].

Figure. 400-MHz ¹H-NMR Spectrum of myxovirescine M₁ obtained by total synthesis

We gratefully acknowledge receipt of stipends from the Fonds der Chemischen Industrie (Germany) given to M. S., A. N., and G. A., from the Ministerio de Educación y Ciencia (Spain) and from the Royal Society (Great Britain), granted to M. M. and F. S., respectively. We thank B. Brandenberg for the high-field NMR spectrum.
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