Total Synthesis of the Formamicin Aglycon, Formamicinone

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Received December 30, 2002

ABSTRACT



The total synthesis of formamicinone (2), the aglycone of formamicin (1), has been accomplished via the late-stage Suzuki cross-coupling of fragments 5 and 6, the macrolactonization of seco ester 14, and the Mukaiyama aldol reaction of aldehyde 3 and methyl ketone 4. An efficient and highly stereoselective second generation synthesis of vinyl iodide 6 is also described.

Formamicin (1) was isolated by Igarashi and co-workers in 1997 from an actinomycete strain (MK27-91F2) obtained from a soil sample.^{1,2} Formamicin possesses strong activity against phytopathogenic fungi and moderate activity toward Gram-positive bacteria. More interestingly, formamicin has strong cytotoxicity against murine tumor cell lines. The stereochemistry of formamicin was assigned by using two-dimensional NMR techniques and confirmed by X-ray structure analysis. Alkaline degradation liberated 2-deoxy-D-rhamnose from C(21), thereby confirming the absolute stereochemistry of $1.^2$

Formamicin is one of the more structurally complex members of the plecomacrolide family,^{3,4} several of which have been synthesized (e.g., elaiophylin (or its aglycone),^{5–8} hygrolidin,⁹ concanamycin F,^{10,11} and bafilomycins A_1 and

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 V_1^{12-17}). We report herein the first total synthesis of the formamicin aglycone, formamicinone (2).

Our synthetic strategy (Scheme 1) called for the C(19)– C(24) tetrahydropyran unit of **2** to be assembled via an aldol



LETTERS 2003 Vol. 5, No. 3 377–379

ORGANIC

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^{10.1021/}ol027569k CCC: \$25.00 © 2003 American Chemical Society Published on Web 01/14/2003

reaction of aldehyde 3^{18} and methyl ketone 4, which in turn would derive from fragments 5 and 6. The C(12–20) fragment 5 is an intermediate in our total synthesis of bafilomycin A₁.^{14,17} A highly efficient and stereoselective second generation synthesis of 5 has been developed¹⁷ by a route utilizing an α -alkoxypropargylation reaction of a chiral aldehyde.¹⁹ We have also previously reported a synthesis of the C(1–11) fragment 6; however, this route suffered from poor selectivity in the aldol reaction used to establish the C(6–7) bond.²⁰ Accordingly, we have developed an improved second generation synthesis of 6 (Scheme 2) en route to the total synthesis of 2.



^{*a*} Key: (a) MOMCl, *i*-PrNEt₂, CH₂Cl₂, 0 → 23 °C; (b) LiBH₄, Et₂O–EtOH, 0 °C, 86% from **7**; (c) (COCl)₂, DMSO, CH₂Cl₂, -70 °C, then **8**; (d) α-ethoxyvinyllithium, THF, -115 °C; (e) PMBBr, KHMDS, Et₃N, THF, 0 °C; (f) 1 N HCl, THF, H₂O, 23 °C, (70% from **8**); (g) 1-propynylmagnesium bromide, THF, -45 → -30 °C, 94%; (h) Bu₃SnH, Pd₂dba₃ (4 mol %), THF, 23 °C, 79%; (i) Me₂BBr, 2,6-DTBMP, CH₂Cl₂, -60 °C, 92%; (j) (*E*)-ethyl-βiodoacrylate, CuTC, Ph₂P(O)OBu₄N, NMP, 92%; (k) DDQ, CH₂Cl₂-H₂O, 0 → 23 °C; (l) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 77% from **13**; (m) NIS, CH₃CN, 0 °C, 87%.

Protection of the hydroxyl group of aldol 7^{20} as a methoxymethyl (MOM) ether followed by reduction²¹ of the



^{*a*} Key: (a) Pd(PPh₃)₄, TlOEt, THF (85%); (b) KOSi(Me)₃, THF; (c) 2,4,6-TCBC, pyridine, THF; (d) DMAP, toluene, 110 °C (62%, from **14**); (e) TFA, H₂O, THF; (f) Dess-Martin, pyridine, CH₂Cl₂ (90%, from **15**); (g) TMS-Cl, Et₃N, LiHMDS, THF, -78 °C; (h) **3**, BF₃-Et₂O, -78 °C, CH₂Cl₂ (65% from **16**); (i) TAS-F, DMF-H₂O (80%).

acyl oxazolidinone unit provided primary alcohol **8** (86%). Oxidation of **8** using the standard Swern protocol²² followed by treatment of the resulting aldehyde with α -ethoxyvinyl-lithium²³ in THF at -115 °C delivered allylic alcohol **9** with \geq 20:1 diastereoselectivity. Protection of the hydroxyl group of this intermediate as a *p*-methoxybenzyl (PMB) ether followed by acidic hydrolysis of the enol ether gave the α -alkoxyketone **10** in 70% overall yield from **8**.

Installation of the C(6) quaternary center was accomplished with >20:1 selectivity by chelate-controlled addition of

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1-propynylmagnesium bromide to **10**.^{24,25} Hydrostannylation of the propargyl alcohol was best accomplished by using Pd₂dba₃ and Bu₃SnH, which provided vinylstannane 11 in 79% yield after two recycles of recovered starting material. Treatment of 11 with Me₂BBr in the presence of 2,6-di-tbutyl-4-methylpyridine (2,6-DTBMP) at -60 °C delivered cyclic acetal 12 in 92% yield.²⁶ Stille-type cross-coupling of 12 and ethyl (E)- β -iodoacrylate promoted by copper(I) thiophene-2-carboxylate (CuTC) then gave enoate 13 in 92% yield.²⁷ The C(7)-PMB ether was removed and replaced by a TES ether (77% from 13), and the vinylsilane was converted into the vinyl iodide by treatment with Niodosuccinimide (NIS) in CH₃CN. Vinyl iodide 6 thus obtained (87%) was identical to material prepared via the first generation sequence.²⁰

The final stages of the synthesis of formamicinone (2) commenced with the modified²⁸ Suzuki coupling²⁹ of **5** and 6, which provided 14 in 85% yield (Scheme 3). Deprotection of the methyl ester was performed by treatment of 14 with KOSiMe₃ in THF.³⁰ Application of the Yamaguchi macrolactonization protocol transformed the seco acid to macrolactone 15 in 62% yield from 14.31 Selective deprotection of the C(19)-TES ether proceeded smoothly upon treatment of 14 with TFA in wet THF. The C(19)-alcohol was then oxidized by using the Dess-Martin periodinane,³² thereby providing methyl ketone 4.

The latter intermediate was converted to the silvl enol ether (LiHDMS, TMS-Cl, Et₃N, THF, -78 °C), which was then

treated with aldehyde **3** and $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -78 °C. This provided aldol **16** in 72% yield with \geq 95:5 selectivity. The stereochemistry of this intermediate was assigned by using our NMR method.³³ Finally, treatment of 16 with TAS-F in wet DMF provided formamicinone 2 in 80% vield.34

Formamicinone has not been described in the literature. Our assignment of synthetic 2 as the aglycon of the natural product follows from the known stereochemistry of fragments 5^{17} and 6^{20} and is strongly supported by comparison of ¹H and ¹³C NMR data for 2 with those of natural formamicin (see Supporting Information). The only significant difference between the two sets of data are for the ¹³C resonances for C(20) and C(21), the site that is glycosylated in the natural product.

Efforts to complete a total synthesis of formamicin are in progress³⁵ and will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM 38436), an Abbott Graduate Fellowship to B.M.S., and a Lavoisier Fellowship to N.B. from the Ministère Français des Affaires Etrangères is gratefully acknowledged.

Supporting Information Available: Procedures and tabulated spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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