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Total Synthesis of the Formamicin Aglycon, Formamicinone

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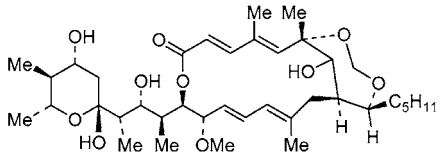
ABSTRACT



formamicinone (**2**)

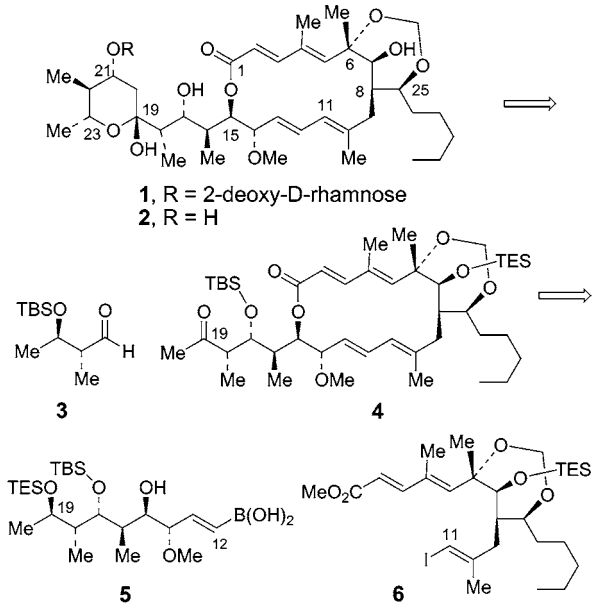
The total synthesis of formamicinone (2), the aglycone of formamicin (1), has been accomplished via the late-stage Suzuki cross-coupling of fragments 5 and 6, the macrolactonization of seco ester 14, and the Mukaiyama aldol reaction of aldehyde 3 and methyl ketone 4. An efficient and highly stereoselective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

Scheme 1. Retrosynthetic Analysis



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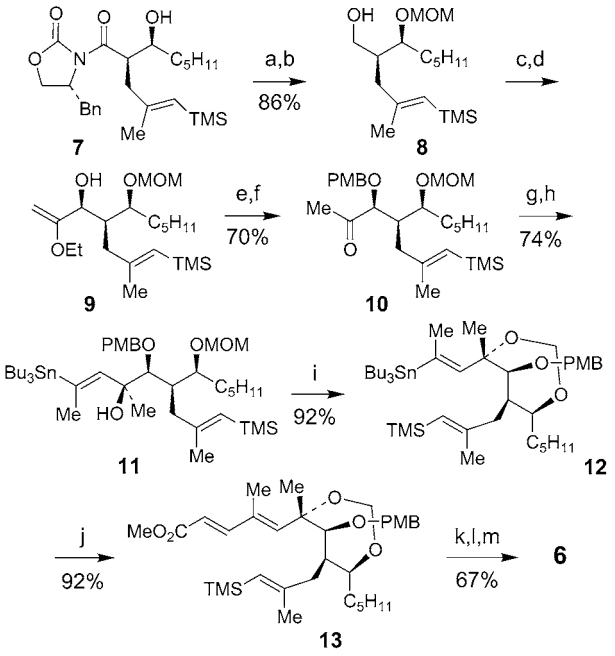
reaction of aldehyde **3**[18] and methyl ketone **4**, which in turn would derive from fragments **5** and **6**. The C(12−20) fragment **5** is an intermediate in our total synthesis of bafilomycin A_1.[14,17] A highly efficient and stereoselective second generation synthesis of **5** has been developed[17] 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**.

Scheme 2. Synthesis of the C(1−11) Fragment **6**[a]

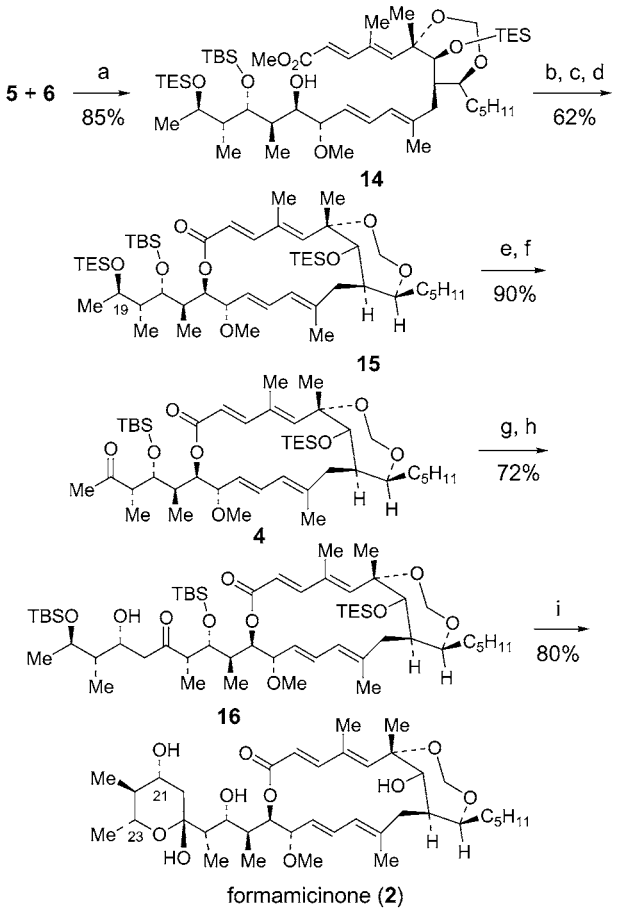


[a] Key: (a) MOMCl, *i*-PrNEt$_2$, CH_2Cl_2, 0 → 23 °C; (b) $LiBH_4$, Et_2O−EtOH, 0 °C, 86% from **7**; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, then **8**; (d) α-ethoxyvinyllithium, THF, −115 °C; (e) PMBBr, KHMDS, Et_3N, THF, 0 °C; (f) 1 N HCl, THF, H_2O, 23 °C, (70% from **8**); (g) 1-propynylmagnesium bromide, THF, −45 → −30 °C, 94%; (h) Bu_3SnH, Pd_2dba_3 (4 mol %), THF, 23 °C, 79%; (i) Me_2BBr, 2,6-DTBMP, CH_2Cl_2, −60 °C, 92%; (j) (*E*)-ethyl-β-iodoacrylate, CuTC, $Ph_2P(O)OBu_4N$, NMP, 92%; (k) DDQ, CH_2Cl_2−H_2O, 0 → 23 °C; (l) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 77% from **13**; (m) NIS, CH_3CN, 0 °C, 87%.

Protection of the hydroxyl group of aldol **7**[20] as a methoxymethyl (MOM) ether followed by reduction[21] of the acyl oxazolidinone unit provided primary alcohol **8** (86%). Oxidation of **8** using the standard Swern protocol[22] followed by treatment of the resulting aldehyde with α-ethoxyvinyllithium[23] in THF at −115 °C delivered allylic alcohol **9** with ≥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

Scheme 3. Synthesis of Formamicinone (**2**)[a]



[a] Key: (a) $Pd(PPh_3)_4$, 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, H_2O, THF; (f) Dess-Martin, pyridine, CH_2Cl_2 (90%, from **15**); (g) TMS−Cl, Et_3N, LiHMDS, THF, −78 °C; (h) **3**, BF_3−Et_2O, −78 °C, CH_2Cl_2 (65% from **16**); (i) TAS-F, DMF−H_2O (80%).

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1-propynylmagnesium bromide to **10**.[24,25] Hydrostannylation of the propargyl alcohol was best accomplished by using Pd_2dba_3 and Bu_3SnH, which provided vinylstannane **11** in 79% yield after two recycles of recovered starting material. Treatment of **11** with Me_2BBr in the presence of 2,6-di-*t*-butyl-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 *N*-iodosuccinimide (NIS) in CH_3CN. 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 modified[28] Suzuki coupling[29] of **5** and **6**, which provided **14** in 85% yield (Scheme 3). Deprotection of the methyl ester was performed by treatment of **14** with $KOSiMe_3$ 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 silyl enol ether (LiHDMS, TMS-Cl, Et_3N, 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 ≥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% yield.[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 ^{13}C 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 ^{13}C 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 progress[35] and will be reported in due course.

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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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