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Studies on the Total Synthesis of Formamicin: Synthesis of the C(1)–C(11) Fragment

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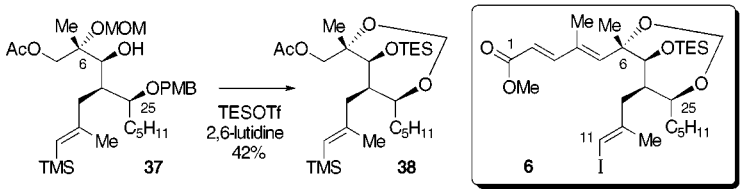
ABSTRACT



An efficient and highly concise synthesis of 6, corresponding to the C(1)–C(11) fragment of formamicin (1), has been accomplished by a route utilizing a diastereoselective lactate aldol reaction to set the C(6) tertiary ether and the TES–OTf mediated transketalization of the C(6) tertiary methoxymethyl ether and the C(25) PMB ether to set the seven-membered methylene acetal unit (see 37 → 38).

Formamicin, **1**, was isolated in 1997 from *Saccharothrix* sp. MK27-91F2, an actinomycete strain that was obtained from a soil sample collected at Setagaya-ku, Tokyo, Japan.[1] Besides showing strong activity against phytopathogenic fungi and moderate activity toward Gram-positive bacteria, formamicin displayed very potent cytotoxicity against murine tumor cell lines in vitro, particularly leukemia cells (IC_{50} = 0.13−0.15 ng/mL for EL4, P388, and L1210 leukemia cell lines). Slightly lower cytotoxicity was observed with IMC carcinoma and S180 sarcoma cells (IC_{50} = 0.29 and 3.45 ng/mL, respectively). The structure of **1** was elucidated by mass spectral and high-field 2D NMR techniques, and the absolute configuration was determined through degradation and X-ray crystal analysis.

Formamicin belongs to the plecomacrolide family of macrolide antibiotics that includes the hygrolidins,[2] concanamycins,[3] and bafilomycins.[4] This natural products family is noted for the presence of a 16- or 18-membered tetraenic macrolactone ring, a conserved, stereochemically rich C(14)−C(23) propionate segment and a six-membered hemiacetal which is often glycosylated at the C(21) hydroxyl with a 2-deoxy-D-rhamnose unit. Formamicin possesses some unique structural features, including the *n*-pentyl chain at C(25) and a C(6) tertiary alcohol and C(25) secondary alcohol that have been incorporated into a seven-membered methylene acetal.

Our retrosynthetic analysis (Figure 1) calls for formamicin to be assembled from the key fragments **2**,[5] **3**, **5**,[6] and **6**. Fragment **5** is an intermediate in our recently completed total synthesis of bafilomycin A_1.[6] We report herein a concise synthesis of **6**, corresponding to the C(1)−C(11) fragment of formamicin (**1**).[7]

Our initial efforts to prepare fragment **6** began with the

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(7) References to total syntheses of other members of the plecomacrolide family are provided in Supporting Information.

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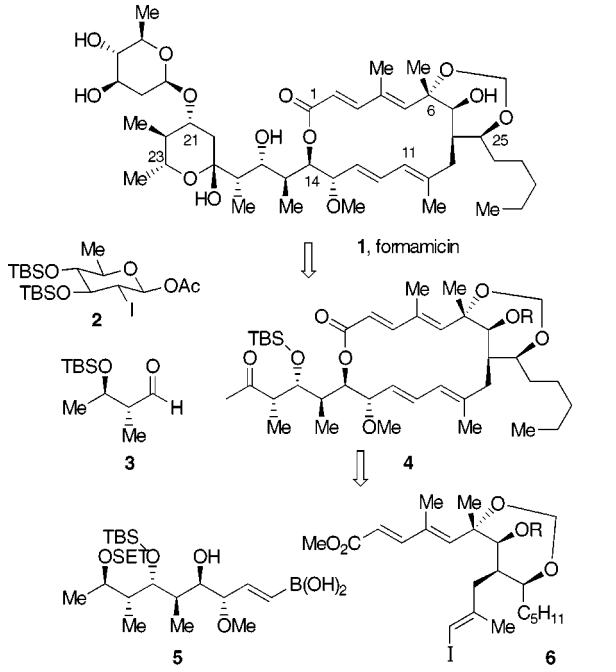


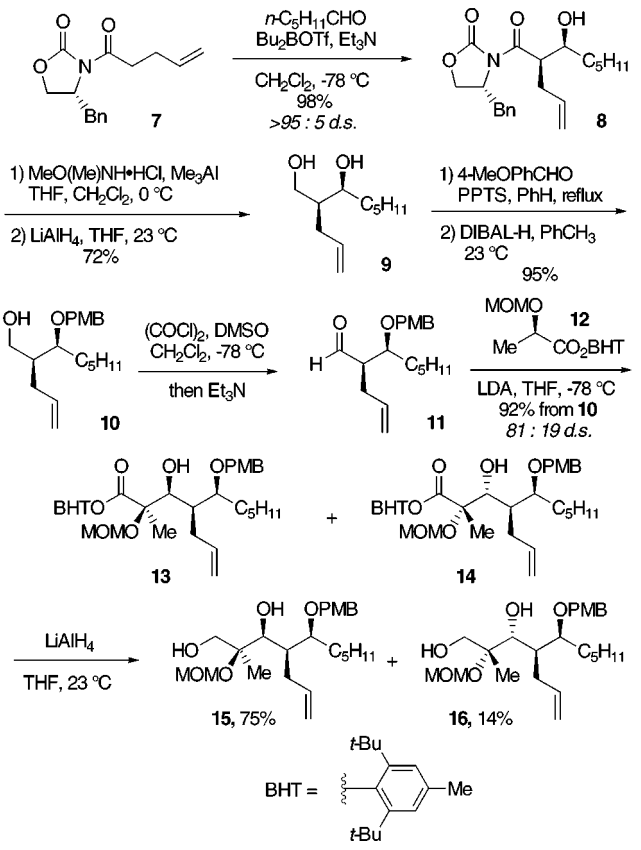
Figure 1. Retrosynthetic analysis.

N-acyl oxazolidinone **7** (Scheme 1).[8] The Bu_2BOTf-mediated asymmetric aldol reaction between **7** and hexanal gave syn-aldol **8** with excellent diastereoselectivity. Following Me_3Al-mediated transamidation of the *N*-acyl oxazolidinone to the corresponding Weinreb amide,[9] $LiAlH_4$ reduction of the amide gave diol **9** in good overall yield. The secondary alcohol was selectively protected as a *p*-methoxybenzyl (PMB) ether by formation of the *p*-methoxybenzylidine acetal followed by DIBAL-H reductive cleavage of the less-hindered C−O acetal bond to afford **10** in excellent yield. Swern oxidation[10] of the primary alcohol provided aldehyde **11**, which was used without purification in the following reaction.

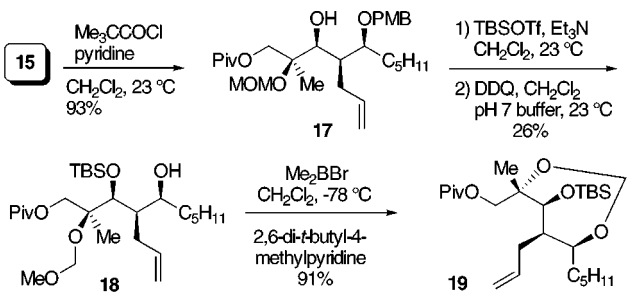
We chose to install the C(6) tertiary and C(7) secondary centers via a diastereoselective *O*-alkyllactate aldol reaction.[11] This strategy allows the tertiary center to be introduced as a methoxymethyl (MOM) ether, in a form suitable for subsequent elaboration into the seven-membered acetal of the natural product. Accordingly, the *Z*(O)-lithium enolate[11b] of the MOM-protected lactate aryl ester **12**[12] was formed by deprotonation with LDA at −78 °C. Addition of aldehyde **11** then gave an 81:19 mixture of aldols **13** and **14** in 91% yield, with the desired all-syn diastereomer **13** predominating.[13] Although **13** and **14** proved inseparable, $LiAlH_4$ reduction of the mixture gave the corresponding mixture of diastereomeric diols **15** and **16**, which were easily separable by flash chromatography.

The primary hydroxyl of the major diol isomer **15** was selectively protected as the pivalate ester **17** (Scheme 2). Attempts to protect the remaining secondary alcohol as a TBS ether were disappointing, giving the desired TBS ether in 32% yield along with 52% of recovered diol **17**.

Scheme 1



Scheme 2



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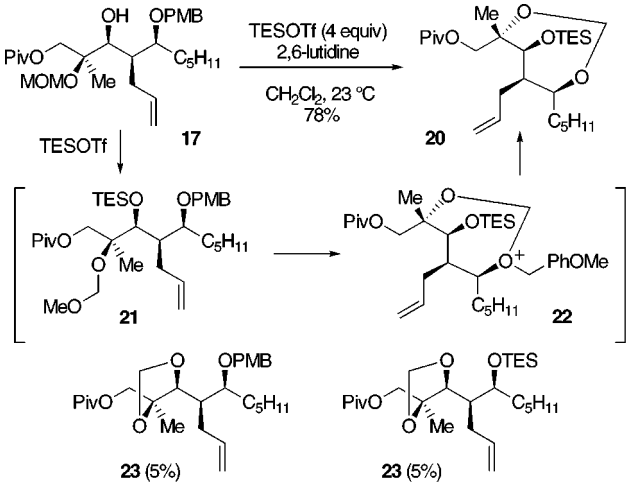
(12) Lactate aryl ester **12** was prepared from methyl *O*-methoxymethyl lactate by a three step sequence of ester hydrolysis (LiOH, MeOH/H_2O), acid chloride formation ($(COCl)_2$, CH_2Cl_2), and condensation with lithium 2,6-di-*tert*-butyl-4-methylphenoxide (THF).[11]

(13) The stereochemical proof of aldol products **13** and **14** is presented in the Supporting Information.

Subsequent DDQ deprotection of the PMB ether afforded alcohol **18** in excellent yield. Treatment of **18** with excess Me_2BBr in the presence of 2,6-di-*tert*-butyl-4-methylpyridine induced a rapid intramolecular transketalization and provided the desired seven-membered acetal **19** in 91% yield.[14]

Although the transketalization strategy proved quite effective, the difficulties encountered in attempted protection of **17** as a TBS ether prompted a search for a more suitable protecting group. Reasoning that the low yield was a result of the steric congestion about the C(7) alcohol, we turned to the sterically smaller TES ether. Accordingly, we were quite pleased to find that treatment of **17** with 4 equiv of commerical grade TESOTf in the presence of 2,6-lutidine (8 equiv) in CH_2Cl_2 not only led to silylation of the alcohol, but also initiated a remarkable sequence of events involving debenzylation of the PMB ether and transketalization of the MOM ether to afford the seven-membered acetal **20** in 78% yield (Scheme 3)! Further investigation revealed that TES

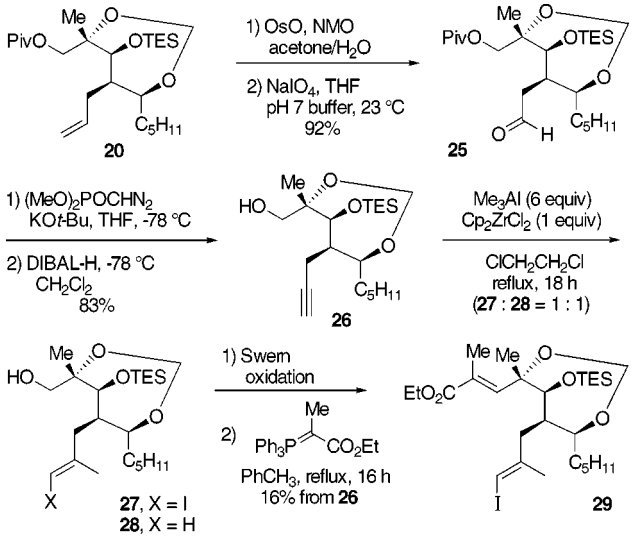
Scheme 3



ether **21** was formed immediately along with the minor byproducts **23** and **24** upon addition of 1 equiv of TESOTf to **17**. Further treatment with 3 equiv of TESOTf resulted in the slower conversion of **21** to acetal **20**. The use of fewer equivalents of additional TESOTf resulted in slower conversion rates and/or incomplete reaction. We believe that the methoxymethyl ether is activated by traces of TfOH in the commerical TESOTf, as use of distilled TESOTf again gave much slower conversion rates. Intramolecular interception of the activated MOM ether by the PMB ether oxygen gives acetal **20** after debenzylation of the oxonium ion **24**.

With an efficient synthesis of **20** in hand, we turned to the elaboration of the trisubsituted vinyl iodide (Scheme 4). Accordingly, the vinyl group of **20** was converted into the corresponding alkyne **26** by oxidative cleavage to aldehyde **25**, Gilbert−Seyferth homologation,[15] and DIBAL-H reduc-

Scheme 4



tion of the pivalate ester. However, the carbalumination[16] of **26** proved extremely sluggish, proceeding only after addition of a large excess of Me_3Al in refluxing dichloroethane over 18 h. The subsequent iodination of the vinylalane intermediate provided an inseparable 1:1 mixture of the vinyl iodide **27** and disubstituted alkene **28** in low mass recovery. Following Swern oxidation of the alcohol,[10] treatment of the resulting aldehyde with $Ph_3P{=}C(Me)CO_2Me$, and HPLC purification, the targeted vinyl iodide **29** was isolated in 16% overall yield from **26**.

Since introduction of the trisubstituted vinyl iodide through a Negishi carbalumination sequence was very inefficient, we redesigned the synthesis to allow for the introduction of the trisubstituted olefin at an earlier stage. Since we anticipated that a vinyl iodide would not be compatible with the $LiAlH_4$ reduction step (e.g., conversion of **13** to **15**), we chose to use a vinyl silane as a vinyl iodide surrogate (Scheme 5). Using the conditions of Danheiser and co-workers,[17] treatment of TMS ether **30** with *t*-BuLi initiated a retro-Brook 1,2-silyl migration to give the corresponding α-silyllithium alkoxide which was trapped with Ac_2O to afford acetate **31**.[18] Treatment of **31** with TBSOTf and Et_2NEt in CH_2Cl_2 over 3 days promoted an Ireland-ester Claisen rearrangement[19] which gave vinyl silane **32** as a single *trans*-olefin isomer. Cleavage of the silyl ester with TMSOK gave the potassium carboxylate salt,[20] which was treated in situ with PivCl to afford the mixed anhydride. Addition of the lithiated oxazolidinone then provided the *N*-acyl oxazolidinone **33** in 54% overall yield from **30**. Asymmetric aldol coupling of **33** with hexanal gave **34** in excellent yield and diastereoselectivity.

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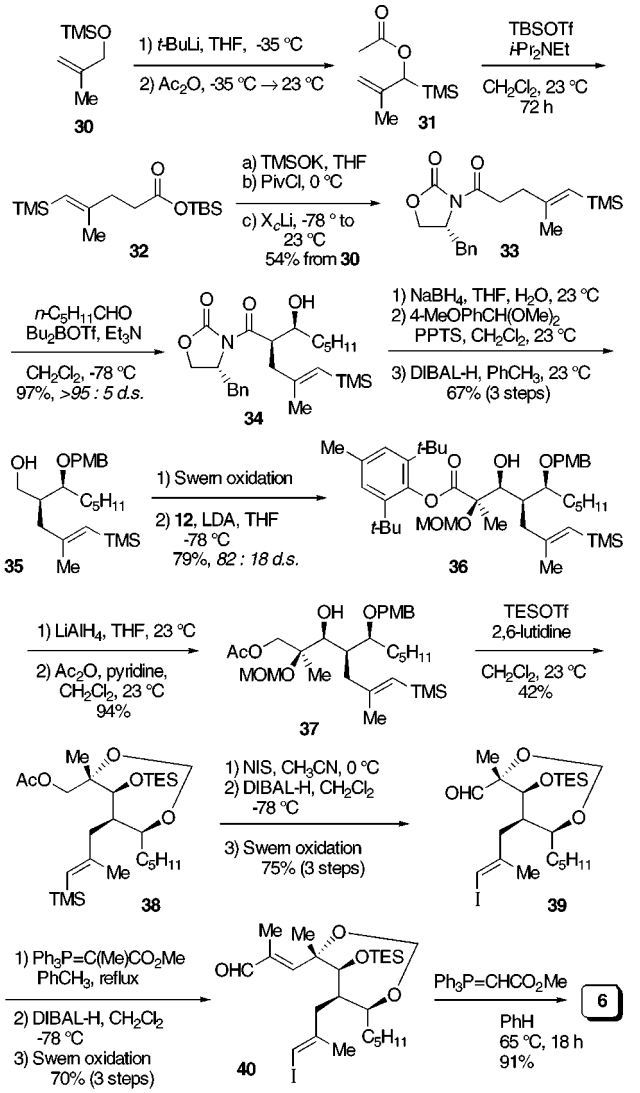
Scheme 5



The oxazolidinone auxiliary was removed by $NaBH_4$ reduction to provide the corresponding diol in 78% yield.[21] Formation of the *p*-methoxybenzylidine acetal followed by DIBAL-H reductive cleavage gave the PMB ether **35** in excellent yield. Swern oxidation of the primary alcohol **35** and condensation of the resulting aldehyde with the lithium enolate of aryl lactate ester **12** provided an 82:18 mixture of aldols with the desired all-syn diastereomer **36** predominating (79% yield). In this case, the diastereomers were separable by HPLC. $LiAlH_4$ reduction of **36** gave the corresponding diol in near quantitative yield. Attempts to protect the primary alcohol as a pivalate ester were unsuccessful. However, the diol could be selectively converted to the monoacetate **37** by treatment with Ac_2O in pyridine and CH_2Cl_2. Treatment of **37** with excess TESOTf and 2,6-lutidine using the procedure developed for the conversion of **17** to **20** afforded the seven-membered acetal **38** in 42% yield.[22]

The vinyl silane was converted to the vinyl iodide (89% yield) as a single olefin isomer by treatment of **38** with *N*-iodosuccinimide. DIBAL-H reductive deprotection of the acetate ester (96% yield) followed by Swern oxidation of the resulting alcohol (88% yield) provided the sterically hindered aldehyde **39** in very good overall yield. Wittig olefination of **39** with $Ph_3P{=}C(Me)CO_2Me$ in toluene at reflux gave the corresponding enoate in 91% yield. DIBAL-H reduction of the ester to the allylic alcohol (91% yield) followed by Swern oxidation (84% yield) gave the unsaturated aldehyde **40** in very good yield. Finally, the remaining olefin was introduced by condensation of aldehyde **40** with $Ph_3P{=}CHCO_2Me$ in warm benzene to provide the *trans*,*trans*-dienoate methyl ester **6** in 91% yield as a single olefin isomer.

In conclusion, we have developed an efficient, stereoselective synthesis of the C(1)−C(11) fragment of formamicin. Further progress toward completion of a total synthesis of this interesting natural product will be reported in due course.

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Supporting Information Available: References to syntheses of other members of the plecomacrolide family, stereochemical assignments of aldols **13** and **14**, and experimental procedures for synthesis of **20**, **30**−**39**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) An additional 18% of material was recovered in form of four minor byproducts **43**−**46**. Interestingly, products containing five membered acetals, analogous to **23** and **24** (Scheme 3), were not observed.