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Published on Web 07/09/2004

Total Synthesis of Formamicin

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Abstract: The enantioselective total synthesis of the cytotoxic plecomacrolide natural product formamicin (**1**) is described. Key aspects of this synthesis include the efficient transacetalation reactions of MOM ethers **28** and **38** to form the seven-membered formyl acetals **29** and **39**, a late-stage Suzuki cross-coupling reaction of the highly functionalized vinyl boronic acid **6** and vinyl iodide **7**, a highly β-selective glycosidation reaction of β-hydroxy ketone **4** with 2,6-dideoxy-2-iodoglucopyranosyl fluoride **3**, and the global desilylation of penultimate intermediate **77** mediated by in situ generated $Et_3N{\cdot}2HF$.

Introduction

The plecomacrolides (formerly known as the hygrolidins)[1] are a large family of natural products, some representative examples of which include the bafilomycins,[2] leucanicidin,[3,4] hygrolidin,[5] the concanamycins,[6] and FD-891[7−9] (Figure 1). These macrolides display potent insecticidal,[3] antiparasitic,[10,11] antifungal,[2] antibacterial,[2] immunosuppressive,[12] cytotoxic,[7] and anthelmintic[13] activities. The family name, plecomacrolide, was inspired by the hemiketal side chain of these molecules and originates from the Greek word "pleco," meaning "I fold."[14] Members of this family are typified by a 16- or 18-membered macrolactone containing four olefin units joined to a side chain which, in most members of the family, contains a six-membered hemiketal unit that is separated from the macrocycle by a three carbon linker (Figure 1). This lactone/linker/hemiketal structural motif forms a distinctive intramolecular hydrogen-bonding network.[14] The presence of this hydrogen bonding network is important to the biological activity of these molecules,[15] although it is not essential.[16]

The biological activity of many members of the plecomacrolide family originates from their ability to act as selective inhibitors of vacuolar H^+-ATPases (V-ATPases).[17,18] V-ATPases are ubiquitous within eukaryotic organisms and utilize energy derived from ATP hydrolysis to maintain a proton gradient for the acidification of organelles.[19] Because of their highly specific inhibition of V-ATPases, the bafilomycins and concanomycins have proven to be useful tools for studying cellular processes involving V-ATPases.[19] Further, the inhibition of the V-ATPases of osteoclasts has been identified as a potential mechanism to prevent bone resorption, the major indication of postmenopausal osteoporosis.[18,20]

Due to the potent and diverse biological activity of the plecomacrolides, this class of natural products has been subjected to substantial efforts directed toward their synthesis. Total syntheses of bafilomycin A_1 have been reported by our laboratory[21,22] as well as by those of Evans,[23] Toshima,[24−26] and Hanessian,[27] while Marshall[28] has reported the total synthesis of bafilomycin V_1. In addition, total syntheses of concanamycin F (the aglycon of concanamycin A) have been reported by Toshima[29,30] and Paterson,[31] while Yonemitsu[32] has reported a total synthesis of hygrolidin.

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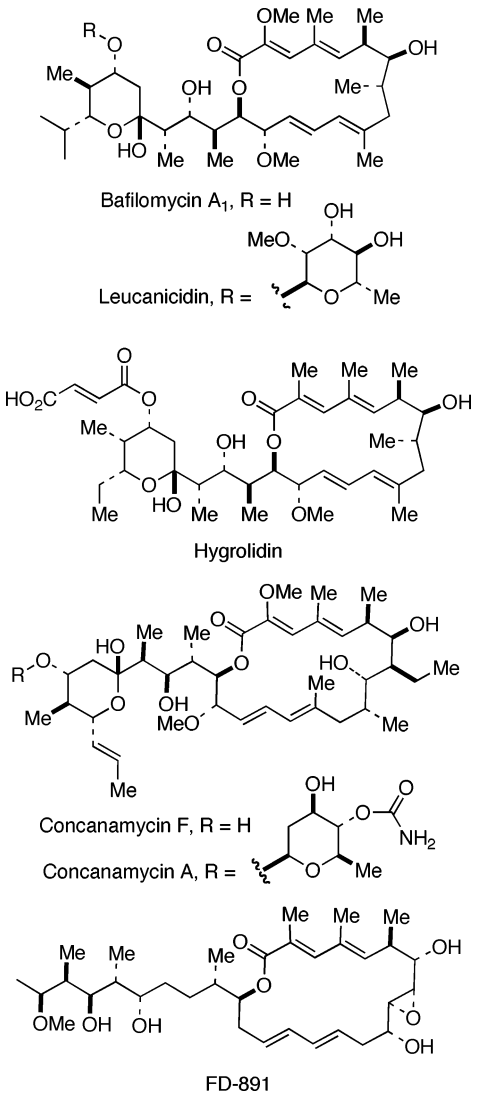

Figure 1. Selected plecomacrolide natural products.

Those members of the plecomacrolide family which contain substitution on the hemiketal pyran hydroxyl, either in the form of acyl or carbohydrate groups, such as occur in hygrolidin and concanamycin A, represent particularly difficult synthetic challenges (Figure 1). These substituents are prone to undergo elimination if the pyran ring opens to reveal the latent β-alkoxy ketone functionality. While Yonemitsu has successfully addressed the introduction of acyl groups in these systems,[32] to the best of our knowledge, no glycosidated member of this family has been successfully prepared.

Formamicin (**1**) is a recently reported plecomacrolide (Scheme 1). This natural product was isolated from the culture broth of *Saccharothrix* sp. MK27-91F2.[33,34] Formamicin (**1**) displays impressive cytotoxicity against a variety of murine tumor cell lines, having IC_{50} values of 0.15−0.13 ng/mL against L1210, EL4, and P388 leukemia cell lines and 3.45 ng/mL against S180 sarcoma cells.[33] Coupled with its impressive cytotoxicity, formamicin (**1**) contains a variety of synthetically challenging architectural elements including the seven-membered formyl acetal unit imbedded within the 16-membered macrocycle, as well as a hemiketal side chain that contains a 2,6-dideoxy-β-glucopyranoside unit. Based on the potent cytotoxicity and unique architectural challenges of formamicin, we initiated a program toward the total synthesis of this natural product and have published two preliminary reports detailing our synthesis of the aglycon, formamicinone (**2**).[35,36] In this paper, we provide a full account of these efforts as well as the completion of the total synthesis of **1** itself.

Synthetic Strategy. In developing a strategy for the synthesis of formamicin (**1**), we recognized the need to address the two most compelling synthetic challenges in the molecule: (i) generation of the highly functionalized seven-membered formyl acetal unit and (ii) introduction of the glycoside onto the C(21) hydroxyl. We hypothesized that the formation of the seven-membered acetal could be achieved through an intramolecular transacetalation reaction (see **20** → **29**). However, introduction of the 2,6-dideoxy-β-glucopyranoside unit proved to be a more challenging problem (as subsequently described).

Previous efforts in our group on the glycosidation of hydroxy hemiketal acceptors (deriving from β,δ-bishydroxy ketones) suggested that a synthetic strategy requiring the introduction of the carbohydrate onto the hemiketal directly would be unsuccessful due to the instability of these acceptors to Lewis acidic glycosidation reaction conditions.[37] Thus, we envisaged that the carbohydrate must be introduced onto the acyclic form of the β-hydroxy ketone side chain (i.e., **4**, Scheme 1). This bond formation represents an especially difficult challenge in carbohydrate chemistry due to the reduced nucleophilicity of hydrogen bound β-hydroxy ketones and the high sensitivity of these systems to Lewis acids.[38] In this context, donor **3** was developed in these laboratories specifically for the β-selective glycosidation of β-hydroxy ketone acceptors (Scheme 1).[38] Therefore, we designed a synthetic strategy in which the fully protected aglycon **4**[36] could be used as an acceptor in a diastereoselective glycosidation reaction with 2,6-dideoxy-2-iodoglucopyranosyl donor **3** (Scheme 1). We anticipated that aglycon **4**[36] could be accessed from the coupling of three fragments: aldehyde **5**,[39] vinyl boronic acid **6** (a key intermediate in our synthesis of bafilomycin A_1),[22,40] and vinyl iodide **7**.[35,36]

In the synthetic direction, our plan was to join fragments **6** and **7** via a late-stage Suzuki cross-coupling reaction and then to append aldehyde **5** via a methyl ketone aldol reaction (Scheme 1). We anticipated that the seven-membered formyl acetal unit of **7** could be prepared through an intramolecular transacetalation reaction. A more pressing concern was to devise a strategy for introducing the four contiguous stereocenters of vinyl iodide **7**. We hypothesized that this could be accomplished through either

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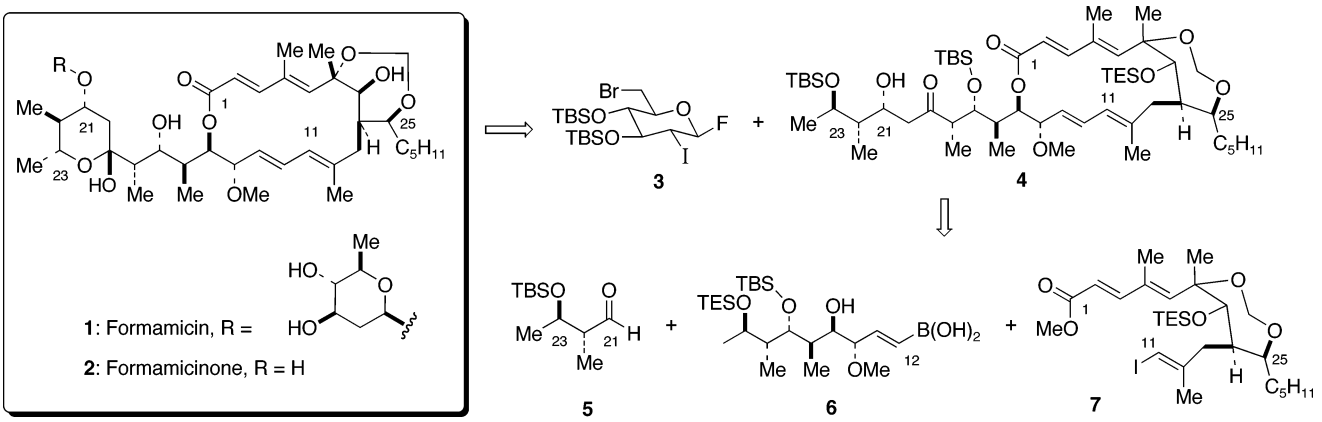
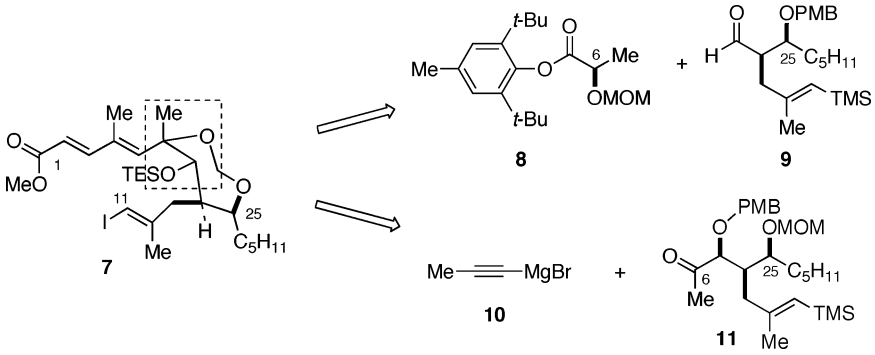
Scheme 1



Scheme 2



a diastereoselective aldol reaction[41−44] of fragments **8** and **9** or via a chelate-controlled addition of Grignard reagent **10** to α-alkoxy ketone **11** (Scheme 2).

Results and Discussion

First Generation Synthesis of Fragment 7. Our first generation synthesis of vinyl iodide **7** focused on the aldol reaction of *O*-alkyl lactate ester **8** and aldehyde **9** to generate the C(6)−C(7)−C(8)−C(25) stereotetrad. Toward this end, 2-methyl-2-propene-1-ol (**12**) was silylated and subjected to a retro-Brook rearrangement (Scheme 3).[45] The resulting alkoxide was then quenched with acetic anhydride to give allyl acetate **13**.[46] Treatment of ester **13** with TBSOTf and Hunig's base promoted an Ireland−Claisen rearrangement[47] to give the corresponding silyl ester which was then hydrolyzed to give carboxylic acid **14** in 70% overall yield from alcohol **12**. Acid **14** was then converted to the mixed pivaloyl anhydride and treated with *N*-lithio-(*R*)-4-benzyl-2-oxazolidinone to provide acyl oxazolidinone **15**. Asymmetric aldol reaction of **15** with hexanal provided the *syn*-aldol product **16** in 97% yield with >95:5 diastereoselectivity. The acyl unit of **16** was then reduced to the primary alcohol with $NaBH_4$[48] in 78% yield. The two hydroxy groups were then differentiated by conversion to the *p*-methoxybenzylidene acetal and subsequent selective, reductive opening via treatment with DIBAL-H.[49] This provided primary alcohol **17** in 67% overall yield from aldol product **16**.

Oxidation of alcohol **17** under standard Swern conditions[50] provided the requisite aldehyde **9** for use in the lactate aldol reaction (Scheme 3). Treatment of aldehyde **9** with the lithium enolate of MOM-protected lactate ester **8**[35] at −78 °C in THF provided an inseparable mixture of aldol products with a diastereomeric ratio of 7.1:1, favoring the desired product **18**.[51] Reduction of the diastereomeric mixture with $LiAlH_4$ provided diols **20** and **21**, which were separable by flash chromatography, in a combined overall yield of 67% from alcohol **17**. Further experimentation showed a striking dependence of the diastereoselectivity of the aldol reaction on the reaction temperature (Table 1). In the optimized protocol, aldehyde **9** was dissolved in THF and added slowly to a −95 °C solution of the lactate enolate, such that the internal temperature of the mixture was not allowed to rise above −92 °C. By carefully controlling the reaction conditions in this way, the diastereoselectivity of the aldol coupling was increased to 11:1 with a concomitant modest increase in the overall reaction efficiency.[51]

At this point, our attention turned to the construction of the seven-membered formyl acetal subunit through an intramolecular transacetalation reaction. During initial efforts directed at the synthesis of fragment **7**, we prepared intermediate **22**[35] (Scheme 4, eq 1). Upon attempting to silylate the free C(7)

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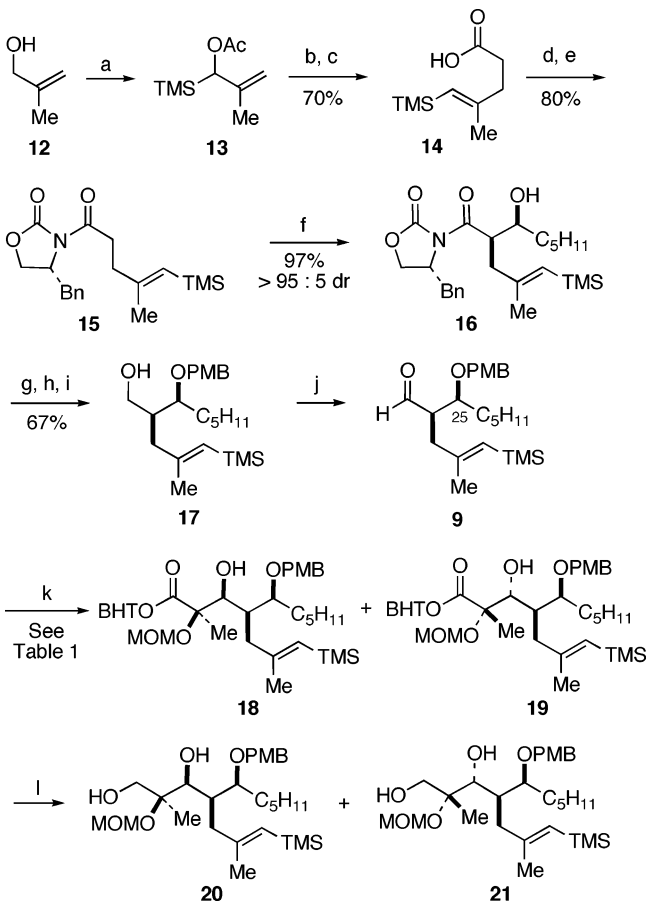
(51) Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

Scheme 3 [a]



[a] Conditions: (a) (i) *n*-BuLi, THF, −78 °C, 15 min; (ii) TMSCl, 2 h; (iii) *t*-BuLi, −78 °C, 2 h; then warm to −40 °C; (iv) Ac_2O; −40 → 23 °C; (b) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2; (c) LiOH, H_2O/MeOH; (d) PivCl, Et_3N, Et_2O; (e) LiXc, THF, −78 °C; (f) Bu_2BOTf, hexanal, CH_2Cl_2, −78 to 0 °C; (g) $NaBH_4$, THF, H_2O, 23 °C; (h) 4-MeOPhCH(OMe)$_2$, PPTS, CH_2Cl_2, 23 °C; (i) DIBAL-H, $PhCH_3$, 23 °C; (j) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (k) **8**, LDA, THF (see Table 1); (l) LAH, THF, 23 °C.

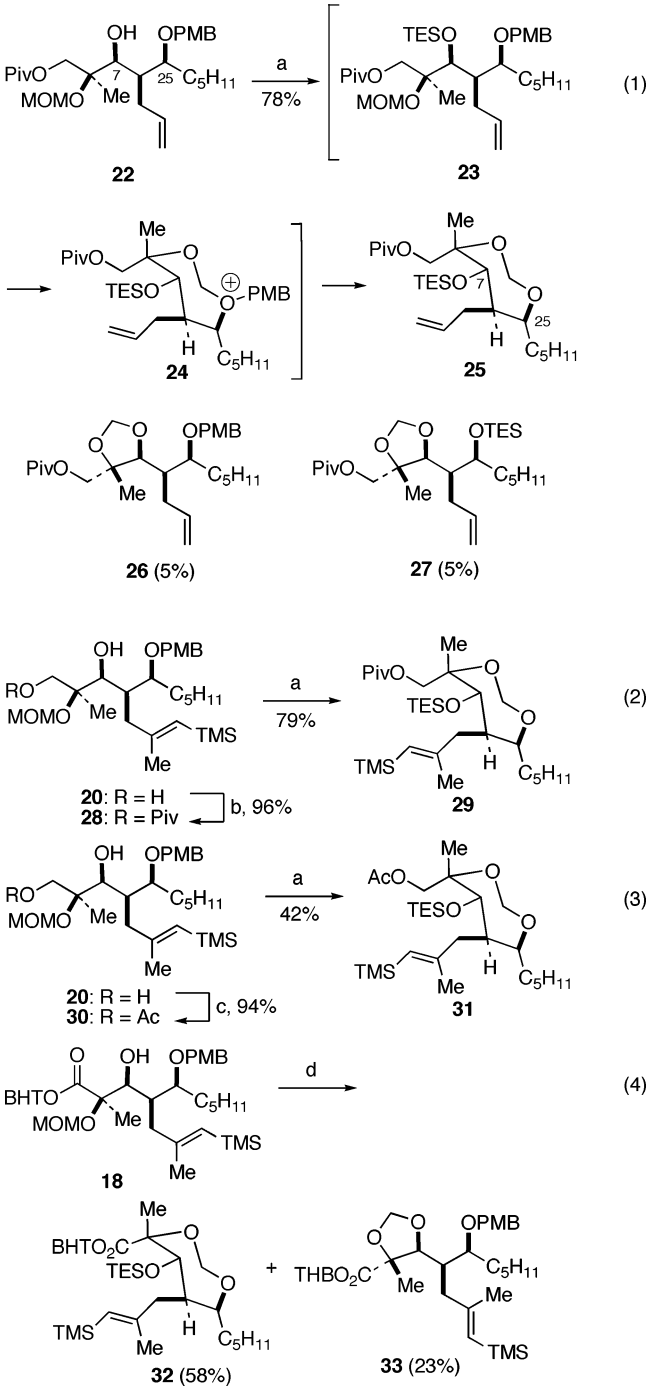
Table 1. Diasteroselectivity of the Lactate Aldol Reaction of **8** and **9** as a Function of Temperature

entry	temperature (°C)	yield (**20** + **21**) (%)	dr (**18**:**19**)
1	−95 → −78	76	11:1
2	−78	67	7.1:1
3	−60	79	5.5:1

alcohol of **22**, we observed that treatment of **22** with 4 equiv of TESOTf directly provided seven-membered formyl acetal **25** in 78% yield![35] Small amounts of the five-membered acetals **26** (5%) and **27** (5%) were also formed under these conditions. Treatment of **22** with 1 equiv of TESOTf showed that the initial intermediate formed was C(7) silyl ether **23**. Rigorous experimentation showed that the transacetalation reaction was promoted by trace triflic acid impurities in the TESOTf.[35] The reaction presumably proceeds by way of oxonium ion **24**, which suffers loss of the *p*-methoxybenzyl cation en route to **25**.

Hoping to capitalize on this efficient approach to formation of the seven-membered acetal, we set out to investigate the generality of this reaction with substrates **28** and **30**, either of which could be converted to fragment **7** (Scheme 4). Treatment of both vinyl silanes **28** and **30** with TESOTf provided the

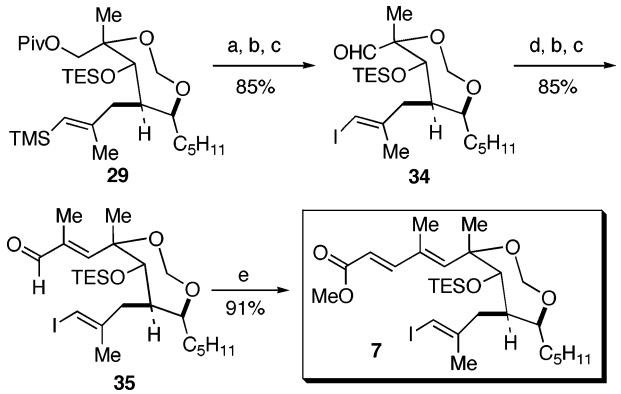
Scheme 4 [a]



[a] Conditions: (a) TESOTf (4.0 equiv), 2,6-lutidine, CH_2Cl_2, 23 °C; (b) PivCl, Py, CH_2Cl_2; (c) Ac_2O, Py, CH_2Cl_2; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, reflux, 24 h.

desired seven-membered acetals **29** and **31**, albeit with strikingly different efficiencies (Scheme 4, eqs 2 and 3). Best results were obtained with pivaloyl ester **28**, which underwent the transacetalation reaction to give **29** in 79% yield. However, we recognized that achieving a similar cyclization on the lactate aldol product **18** (Scheme 3) would shorten the synthetic route to fragment **7** by two steps. However, the reaction of *β*-hydroxy ester **18** with TESOTf was both significantly slower and less efficient than that of **28**, producing the desired product **32** in only 58% yield along with 23% of the five-membered acetal **33** (Scheme 4, eq 4). Therefore, from the perspective of overall

Scheme 5 [a]



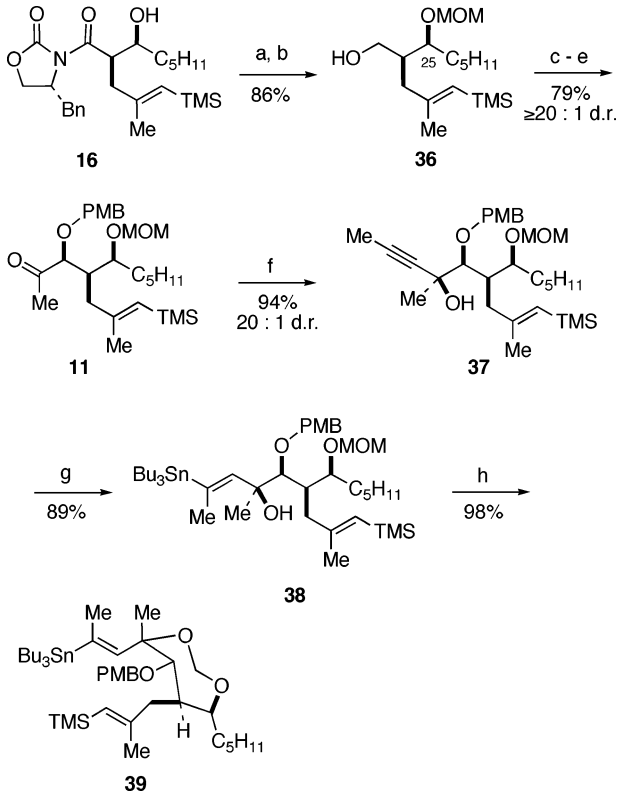
[a] Conditions: (a) NIS, CH_3CN, 0 °C; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (d) $Ph_3P{=}C(Me)CO_2Et$, $PhCH_3$, reflux; (e) $Ph_3P{=}CHCO_2Me$, PhH, 65 °C, 18 h.

synthetic efficiency, it was more advantageous to utilize pivaloyl ester **29** as an intermediate in the synthesis of vinyl iodide **7**.

Treatment of **29** with NIS effected the conversion of the vinyl silane to the corresponding vinyl iodide (Scheme 5). Removal of the pivaloate ester was achieved through treatment of the ester with DIBAL-H. Oxidation of the resultant alcohol under standard Swern oxidation conditions provided aldehyde **34**. Homologation of **34** via Horner−Wadsworth−Emmons reaction[52] with $Ph_3P{=}C(Me)CO_2Et$ provided the corresponding enoate, which was reduced to the primary alcohol using DIBAL-H and then oxidized under Swern conditions to give aldehyde **35**. Finally, olefination of aldehyde **35** with $Ph_3P{=}CHCO_2Me$ completed the synthesis of the C(1)−C(11) fragment **7**. Overall, this synthesis of vinyl iodide **7** proceeded in 23 linear steps and 16% overall yield.

Second Generation Synthesis of Fragment 7. In parallel to our development of the lactate aldol approach to fragment **7**, investigations were also conducted to develop a synthesis based on the chelate-controlled addition of an alkynyl nucleophile to aldehyde **11**. In our original lactate aldol strategy, the MOM ether necessary for the transacetalation reaction had been introduced at the C(6) alcohol. However, we recognized that placing the MOM group on the C(25) alcohol might provide the opportunity to shorten the synthetic sequence and minimize protecting group manipulations. Toward this end, protection of aldol **16** as a MOM ether followed by reductive removal of the chiral auxiliary by using $LiBH_4$[53] provided primary alcohol **36** (Scheme 6). Alcohol **36** was then subjected to standard Swern oxidation conditions followed by aqueous workup. The crude aldehyde was then coupled with α-lithio ethyl vinyl ether[54] at −118 °C to give the corresponding carbonyl addition product with ≥20:1 diastereoselectivity. Protection of the resulting alcohol using *p*-methoxybenzyl bromide (PMBBr) followed by hydrolysis of the enol ether with 0.1 N HCl provided α-alkoxy ketone **11** in 79% overall yield for the four steps. Methyl ketone **11** was then coupled with 1-propynylmagnesium bromide under chelate-controlled conditions,[55,56] thereby generating the desired tertiary alcohol **37** in 94% yield with >20:1 diastereoselectivity.[51]

Scheme 6 [a]



[a] Conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (b) $LiBH_4$, EtOH, Et_2O, 0 °C; (c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (d) EtO(Li)C=CH_2, THF, −118 °C, (e) KHMDS, Et_3N, PMBBr, THF then 1 N HCl; (f) $CH_3C{\equiv}C{-}MgBr$, THF, −45 °C; (g) Bu_3SnH (10 equiv), (*Po*-$Tol_3)_2PdCl_2$ (10 mol%), THF; (h) Me_2BBr, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 → −50 °C.

We next explored transition-metal-catalyzed chain extension reactions of **37**. Initial experiments[36] showed that hydrostannation of alkyne **37** could be accomplished using $Pd_2dba_3{\cdot}CHCl_3$ (4 mol %) and Bu_3SnH (20 equiv).[57] Unfortunately, full consumption of alkyne **37** under these conditions did not occur, requiring that recovered starting material be recycled twice to achieve a synthetically useful 79% yield of vinyl stannane **38**. A more efficient approach was eventually found which utilized $(o\text{-}Tol_3P)_2PdCl_2$ as the hydrostannation catalyst.[58] Use of this more reactive catalyst allowed a reduction in the equivalents of Bu_3SnH (10 equiv) and induced complete consumption of alkyne **37**. In this way, vinyl stannane **38** was obtained in 89% yield (Scheme 6).

With vinyl stannane **38** in hand, formation of the seven-membered formyl acetal was investigated. To our delight, treatment of alcohol **38** with Me_2BBr[59] at −78 °C promoted the transacetalation and provided cyclic acetal **39** in 98% yield (Scheme 6).

We hoped that a more direct approach to fragment **7** could be achieved by avoiding the use of the PMB protecting group in **37**. To investigate this possibility, substrates **40** and **44** (Scheme 7) were prepared from alcohol **36**.[60] Surprisingly, treatment of **40** with 2 equiv of TESOTf did not produce the

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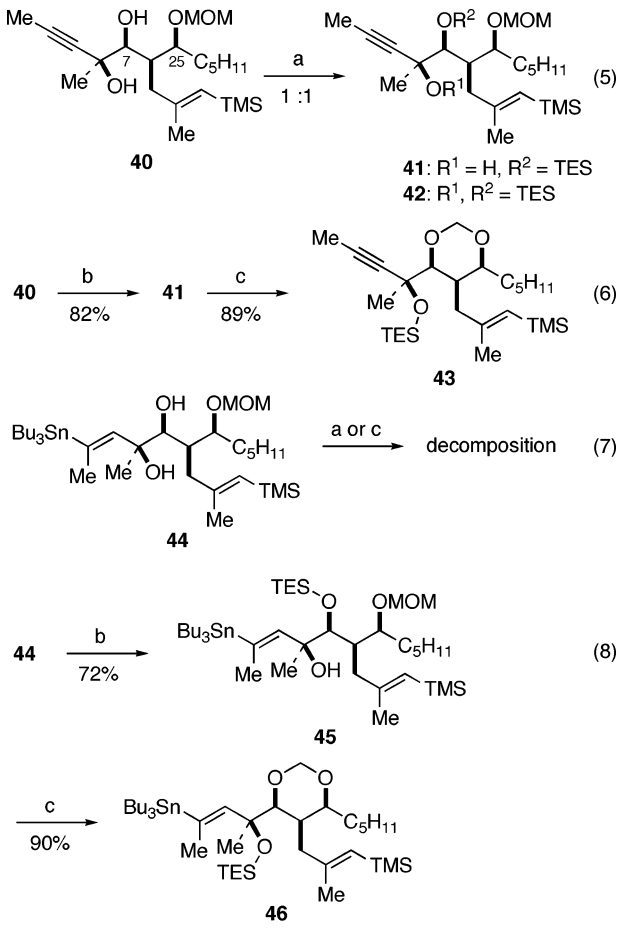
Scheme 7 [a]

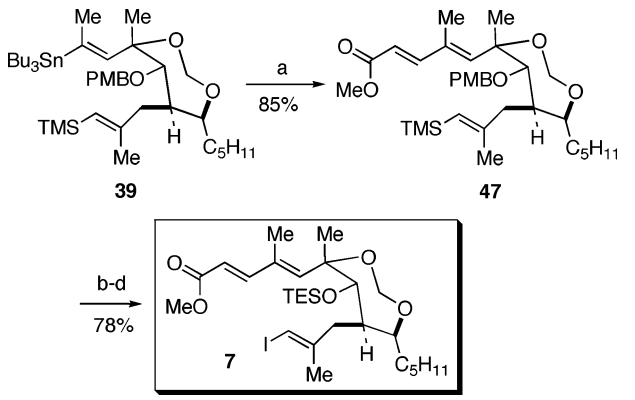


[a] Conditions: (a) TESOTf (2 equiv), 2,6-lutidine, CH_2Cl_2, 0 → 23 °C; (b) TESOTf (1 equiv), 2,6-lutidine, CH_2Cl_2, 0 °C; (c) Me_2BBr, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −70 to −60 °C.

expected cyclization product but instead gave a 1:1 mixture of the mono- and bis-silylated products **41** and **42** (Scheme 7, eq 5). Treatment of C(7) TES ether **41** with Me_2BBr gave six-membered acetal **43** with concomitant silyl migration (Scheme 7, eq 6).

Recalling that the cyclization of C(5) pivaloate ester **28** had been more efficient than that of C(5) acetate **30** (Scheme 4, eqs 2 and 3), we hypothesized that increasing the steric environment around the C(5) carbon might improve the chemoselectivity of the cyclization. Accordingly, we attempted to form the seven-membered acetal from vinyl stannane **44** (Scheme 7, eq 7). Vinyl stannane **44** is analogous to our previous PMB ether **38** which had cyclized with both high efficiency and chemoselectivity (Scheme 6). However, treatment of alcohol **44** with either TESOTf or Me_2BBr lead only to decomposition (Scheme 7, eq 7). A stepwise approach, in which the C(7) alcohol of **44** was first converted to TES ether **45** and then subsequently exposed to Me_2BBr, also did not provide the seven-membered acetal product (Scheme 7, eq 8). Instead, the six-membered acetal **46**, in which the C(7) TES group had undergone a silyl migration to the tertiary alcohol, was isolated in 90% yield.

Scheme 8 [a]



[a] Conditions: (a) methyl (*E*)-3-iodopropenoate (1.9 equiv), copper(I) 2-thiophene carboxylate (CuTC, 2 equiv), tetrabutylammonium diphenylphosphinate (1.1 equiv), NMP; (b) DDQ, pH = 7 buffer/CH_2Cl_2, 0 °C; (c) TESOTf, 2,6-lutidene, CH_2Cl_2, 0 °C, 78% for two steps; (d) NIS, CHCN, 96% to quant..

It was anticipated that the carbon skeleton of fragment **7** could be completed through a Stille cross-coupling[61] reaction between vinyl stannane **39** and methyl (*E*)-3-iodopropenoate[62] to give dienoate **47** (Scheme 8). Initial attempts to achieve this coupling under a variety of Pd(0)-catalyzed conditions proved to be unsuccessful. However, combined use of copper(I) 2-thiophene carboxylate (CuTc)[63] and the trialkyltin halide scavenger tetrabutylammonium diphenylphophinate[64] eventually proved to be effective (Scheme 8). Initial experimentation, in which the vinyl stannane and vinyl iodide were mixed prior to addition of CuTc, showed that homocoupling of methyl (*E*)-3-iodopropenoate was a competitive background reaction. Facile homocoupling of vinyl iodides upon exposure to CuTc has been previously observed by Liebeskind, who has suggested that, in some systems, oxidative insertion of Cu (I) with alkenyl iodides is facile and occurs more rapidly than transmetalation with the vinyl stannane.[63] This undesired reaction could be minimized by syringe pump addition of a solution of the vinyl iodide into a mixture of vinyl stannane **39** and CuTc.

However, as the reaction scale was increased to >100 mg of vinyl stannane **39**, proteodestannylation also became a competitive side reaction. Careful experimentation showed that this byproduct arose from proton abstraction from the reaction solvent at the stage of a putative vinyl copper species produced by transmetalation of stannane **39**.[63] This observation suggests that in the reaction of **39** with CuTc the rate of transmetalation of the stannane is relatively fast at the beginning of the reaction time scale but slows as the reaction progresses to a more moderate rate.[65] Suppression of this second nonproductive reaction pathway, while simultaneously limiting the degree to which methyl (*E*)-3-iodopropenoate underwent homocoupling, could be achieved by adding ∼0.2 equiv of methyl (*E*)-3-iodopropenoate to the stannane prior to addition of CuTc.

(60) Compound **40** was prepared from **36** by the following sequence: (a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (b) EtO(Li)C=CH_2, THF, −118 °C; then 1 N HCl 0 °C, 88%, >20:1 dr; (c)**10**, THF, −45 °C, >20:1 dr. Compound **44** was generated from **40** via hydrostannation: Bu_3SnH (10 equiv), Pd_2dba_3·$CHCl_3$ (4 mol %), THF (77%).

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(65) While the exact cause of the purported difference in rate of transmetalation of **39** with CuTc is not known, it should be noted that this reaction is heterogeneous. If transmetalation is occurring at the surface of the solid CuTc, this could explain the variation in reaction rate, as well as the differences in the efficiency of the coupling depending on the scale of the reaction.

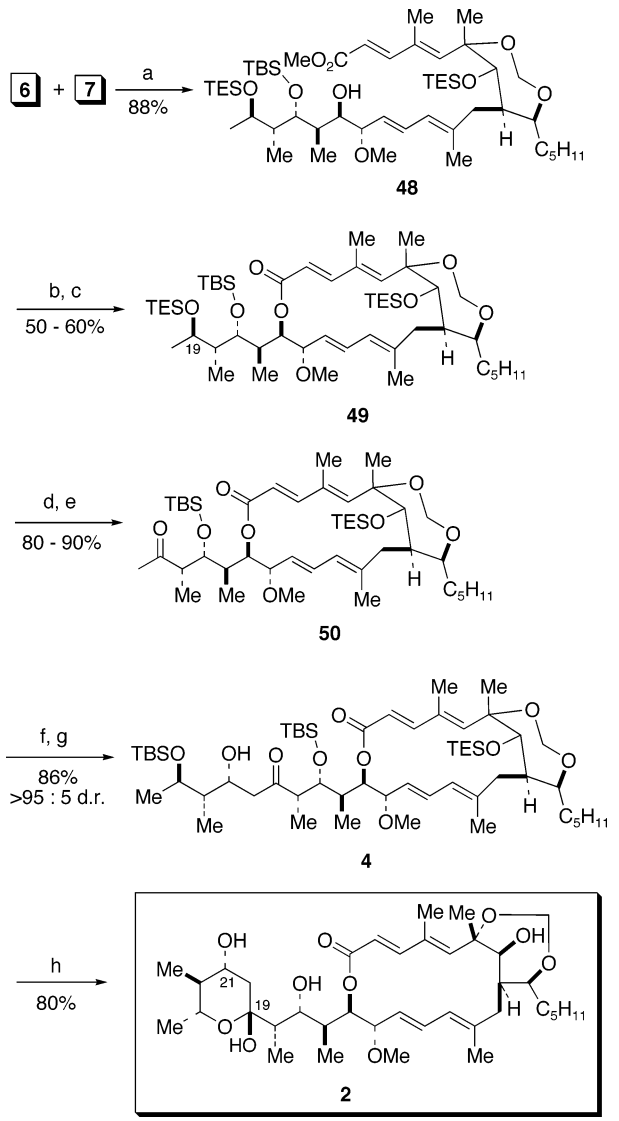
Subsequent syringe pump addition of the remaining solution of the vinyl iodide (1.7 equiv) to the reaction mixture over 15−20 min then provided **47** in 85% yield. This optimized experimental protocol could be used to conduct this cross-coupling on a multigram scale.

Dienoate **47** was then elaborated to fragment **7** by a two-step modification of the C(7) protecting group and conversion of the vinyl silane to the iodide via treatment with NIS at 0 °C (Scheme 8). Using the approach shown in Schemes 6 and 8, this second synthesis of fragment **7** required 21 linear steps and proceeded with an overall yield of 20%. The diastereoselectivity of the least selective step was 20:1.

Synthesis of Formamicinone. With access to synthetically useful quantities of vinyl iodide **7**, elaboration of this fragment to the formamicin aglycon, formamicinone (**2**), proceeded smoothly. Suzuki cross-coupling of vinyl iodide **7** and vinyl boronic acid **6**[22,40] occurred readily under Pd(0)-catalyzed conditions in the presence of either TlOEt[66] or Tl_2CO_3[67] to give tetraene **48** in 88% yield (Scheme 9). Deprotection of the methyl ester **48** with $KOSiMe_3$[68] gave the seco acid. The carboxylic acid was then subjected to Yamaguchi macrolactonization[69] which produced lactone **49** in a 50−60% yield from ester **48**. The oxidation state of C(19) was then adjusted by selective deprotection of the C(19) TES ether under acidic conditions and subsequent oxidation of the C(19) hydroxyl with Dess−Martin periodinane.[70] This produced methyl ketone **50** in 80−90% yield over two steps. Mukaiyama aldol coupling of **50** and aldehyde **5**[39] proceeded with excellent diastereoselectivity to give alcohol **4** in 86% yield and >95:5 diastereomeric ratio (dr).[51] The stereochemistry of the β-hydroxy ketone was assigned by NMR methods.[71] Deprotection of aldol **4** using tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) in DMF/H_2O provided the aglycon of the natural product, **2**, in 80% yield.[72] Comparison of the ^1H and ^{13}C NMR data of **2** and formamicin (**1**) showed excellent agreement, with the only noticeable differences in chemical shifts being those for the C(20) and C(21) residues, the site at which the natural product is glycosylated.

Studies of the Glycosidation Reaction. The next issue to be addressed was the introduction of the 2,6-dideoxyglucopyranoside unit, which we anticipated would be best accomplished using **4** as the acceptor (vide infra). While methods for the β-selective glycosidation of β-hydroxy carbonyl compounds had been reported in the literature when we began our own studies in this area,[38] a general method providing both high efficiency and selectivity had yet to be established. The weakened reactivity of the β-hydroxy group due to intramolecular hydrogen bonding with the carbonyl moiety[73] and

Scheme 9 [a]



[a] Conditions: (a) $Pd(PPh_3)_4$ (cat.), Tl_2CO_3, THF/H_2O 3:1; (b) KOTMS, Et_2O/THF; (c) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, reflux, 12 h; (d) AcOH/H_2O/THF 6:1:6; (e) Dess−Martin periodinane, pyridine, CH_2Cl_2; (f) LHMDS, Et_3N/TMSCl, THF, −78 °C; (g) **5**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (h) TASF, H_2O, DMF.

the instability of β-hydroxy and β-alkoxy carbonyl derivatives to Lewis acidic reaction conditions (vide infra) are most likely the sources of difficulty inhibiting the development of a general protocol. Among the few reports of such glycosidations in the chemical literature, the following three instances are illustrative. The glycosidation of a β-hydroxy ketone using a 2-deoxyglucopyranosyl fluoride[74,75] donor was demonstrated by Tatsuta and Kinoshita to proceed with only modest selectivity and low efficiency (30% yield).[76,77] Use of both a 2-deoxyglucopyranosyl phosphite and a 2-deoxyglucopyranosyl bromide donor in an attempt to effect the β-selective glycosidation of a similar β-hydroxy ketone by Paterson also resulted in low isolated yields

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(73) Results from our laboratories suggest that β-hydroxy ketones such as **58**, which are capable of intramolecular hydrogen-bonding, are far less reactive than alcohol acceptors such as **60** and **62**. However, a similar hydrogen-bonding pattern has been reported to increase the nucleophilicity of hydrogen-bound acceptors; Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R. *J. Org. Chem.* **2001**, *66*, 2327.
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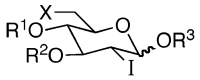
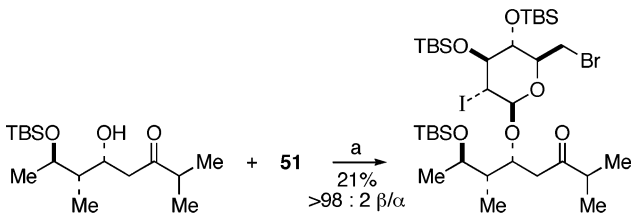
Scheme 10 [a]

51: X = Br, R^1 = TBS
52: X = Br, R^1 = TBDPS
53: X = H, R^1 = TBS



54: X = Br, R^1 = R^2 = TBS, R^3 = -C(NH)CCl_3
55: X = Br, R^1 = R^2 = TBDPS, R^3 = -C(NH)CCl_3
56: X = H, R^1 = R^2 = TBDPS, R^3 = -C(NH)CCl_3
57: X = Br, R^1 = ClAc, R^2 = TES, R^3 = -P(O)$(OBn)_2$

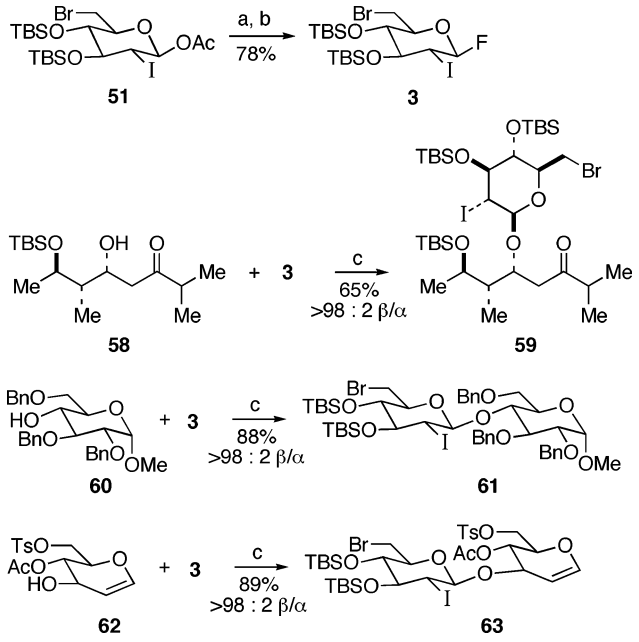


[a] Conditions: (a) TBSOTf (0.3 equiv), CH_2Cl_2, −78 °C.

(21−39%) and proceeded with only modest β-selectivity ($\leq$2.5:1 β/α).[77] Finally, Evans has also reported a β-selective glycosidation reaction of a β-hydroxy Weinreb amide acceptor with a 2-deoxyglycosyl acetate donor (70%, 4:1 β/α).[78] The authors noted that equilibration of the α-glycoside to the β-glycoside could be achieved by resubjection to the reaction conditions. Further, the selectivity was highly dependent upon both reaction conditions and substituents on the donor.

Our laboratory has recently reported methodology for the stereoselective synthesis of 2-deoxy-β-gluco- and galactopyranosides using 2-deoxy-2-iodo- and 2-deoxy-2-bromoglucopyranosyl[79−82] and galactopyranosyl[83,84] acetates and trichloroacetimidates. After generation of the β-glycosidic linkage, the C(2)-halogen directing groups can be easily excised from the products by reduction with Bu_3SnH.[85] Given the high selectivity and efficiency of these reactions, we initially hoped that these 2-deoxy-2-iodo donors could be used to achieve the β-selective glycosidation of β-hydroxy ketones. Subsequently we examined the glycosidation of model β-hydroxy ketone **58**[38] using a variety of 2-deoxy-2-iodoglucopyranosy donors (**51**−**57**)[38,79,80] (Scheme 10) under a variety of Lewis acidic conditions (TMSOTf, $BF_3{\cdot}OEt_2$, $TrClO_4$,[78] K10 clay,[86] $LiClO_4$,[87] LiOTf[88]). However, these initial attempts led only to decomposition of β-hydroxy ketone **58**. Control experiments showed that the decomposition of ketone **58** in the presence of TMSOTf at temperatures ranging from −78 to −30 °C occurred within 20 min. However, use of the milder activator TBSOTf and donor **51** was successful, providing β-glycoside **59** with high stereoselectivity (>98:2 β/α) but in low efficiency (21%, Scheme 10).[51]

Scheme 11 [a]



[a] Conditions: (a) H_2NNH_2, MeOH−Et_2O, 0 °C; (b) DAST, CH_2Cl_2, 0 °C; (c) $SnCl_2$, $AgClO_4$,Et_2O, 4 Å MS, −15 °C, 20−30 min.

In view of the sensitivity of both the acceptors and products to Lewis acidic reaction conditions, we anticipated a more efficient glycosidation reaction could be realized if a milder set of activation conditions was employed. Recalling the successes of Tatsuta and Kinoshita as well as Paterson using Ag(I) salts to achieve activation of 2-deoxyglucopyranosyl fluorides[76] and bromides[77] under mild conditions, we next prepared 2-deoxy-2-iodoglucopyranosyl fluoride **3**.[89,90] Selective deprotection of the anomeric acetate of **51** using aqueous hydrazine[91] followed by reaction of the hemiacetal with diethylaminosulfur trifluoride (DAST) provided β-glucopyranosyl fluoride **3** in 78% yield (Scheme 11).[92,93] Activation of fluoride donor **3** in the presence of β-hydroxy ketone **58** using Mukaiyama's conditions[94] ($SnCl_2/AgClO_4$) at −15 °C in ether provided β-glycoside **59** in 65% yield with >98:2 β/α selectivity.[51] Further experiments showed that glycosidation reactions of fluoride donor **3** with a variety of acceptors were highly β-selective (Scheme 11).[51] Additionally, these reaction conditions were sufficiently mild to accommodate even highly sensitive acceptors such as glycal **62**.[95,96]

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(89) A single example using a 2-deoxy-2-iodoglucopyranosyl fluoride donor in the glycosidation of cyclohexanol has been reported: Nishimura, S.; Washitani, K. (Sumitomo Pharmaceuticals Co., Ltd., Japan) Stereoselective Production of Glycosyl Compound. Japanese Patent 09241288, 1997.
(90) Thiem has studied 2,6-dideoxy-2,6-dibromoglucopyranosyl fluorides and 2,6-dideoxy-2,6-dibromomannopyranosyl fluorides in the synthesis of oligosaccharides using a mixture of TiF_4 and $AgClO_4$ as the promoter. Reactions of the 2,6-dideoxy-2,6-dibromoglucopyranosyl fluorides gave yields of 43−75% and selectivities ranging from 1:1 to 7:1 β/α. The reaction selectivity showed significant dependence on the solvent, the fluoride substituent stereochemistry (α vs β), and identity of the acceptor. For the original report, see: Jünneman, J.; Lundt, I.; Thiem, J. *Liebigs Ann. Chem.* **1991**, 759.
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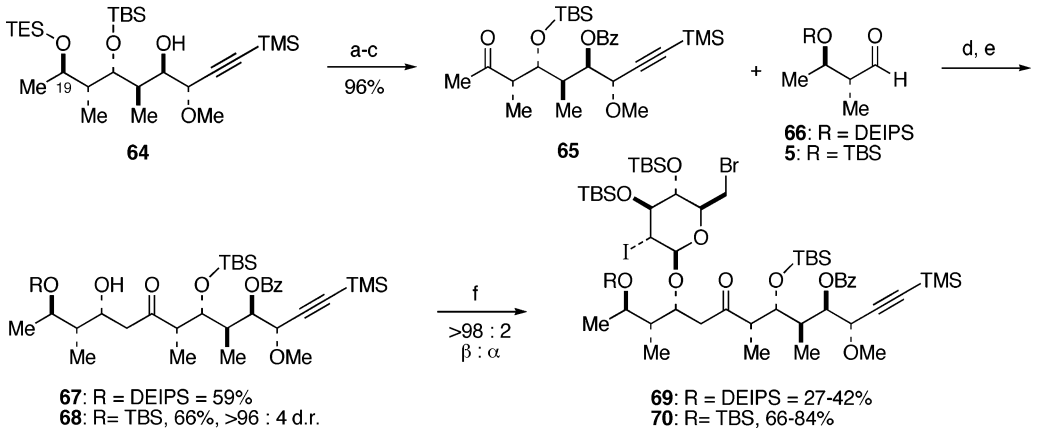
Scheme 12 [a]



[a] Conditions: (a) BzCl, DMAP, Et_3N, CH_2Cl_2, quant.; (b) AcOH/THF/H_2O 6:6:1; (c) Dess−Martin periodinane, pyridine, CH_2Cl_2, 96% over two steps; (d) LHMDS, Et_3N/TMSCl, THF, −78 °C; (e) **66** or **5**, BF_3·OEt_2, CH_2Cl_2; (f) **3**, $SnCl_2$, $AgClO_4$,Et_2O, 4 Å MS, −10 °C.

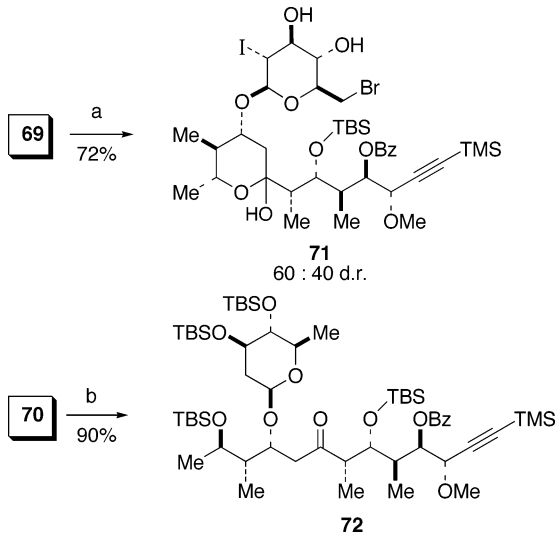
To determine the suitability of this glycosidation reaction for use in our synthesis of formamicin (**1**), we next examined the glycosidation reaction of donor **3** using model compounds **67** and **68** (Scheme 12). Preparation of the **67** and **68** commenced with compound **64**, which is an intermediate in the synthesis of vinyl boronic acid **6**.[22,40] Benzoylation of the C(15) hydroxyl followed by deprotection of the C(19) TES protecting group under acidic conditions and oxidation of the resultant alcohol with Dess−Martin periodinane provided methyl ketone **65**. Mukaiyama aldol coupling of **65** and aldehydes **66** and **5** proceeded with excellent diastereoselectivity to give aldols **67** and **68** in 59% and 66% yields, respectively. Glycosidation of these β-hydroxy ketones using 2-iodoglucopyranosyl fluoride donor **3** proceeded with >98:2 β-selectivity and gave β-glycosides **69** (27−42% yield) and **70** (66−84% yield).[51]

Studies of the Deprotection Sequence. Satisfied that fluoride donor **3** could be used to install the 2,6-dideoxy pyranoside of formamicin, we turned our attention to investigating conditions to effect desilylation of the final intermediate. For these studies we chose to use model compounds **71** and **72**. Synthesis of glycoside **71** was achieved in 72% yield from aldol **69** by selective deprotection of the DEIPS ether via treatment with 1% HF·KF/AcOH in THF at 33 °C over 4 days (Scheme 13). Model glycoside **72** was easily prepared from **70** by way of reductive removal of the C(2′)-iodo and C(6′)-bromo substituents using Bu_3SnH[85] in 90% yield.

Initial investigations to develop a set of global desilylation conditions applicable to the synthesis of formamicin focused on hemiketal **71** (Table 2). We hoped that the hemiketal unit would serve to mask the β-alkoxy ketone and thus suppress elimination of the 2,6-dideoxyglucopyranoside unit during the deprotection step. Having found that TASF was highly effective in the desilylation of protected aglycon **4**, it was most surprising that treatment of **71** with TASF provided only elimination products **75**, even under buffered[97] conditions (Table 2, entries 1 and 2)!

More extensive studies were performed using **72**, which is available with better efficiency than **71** (cf., Schemes 12 and 13). Subjection of **72** to a variety of standard desilylation conditions including TBAF, TBAF/AcOH, and TBAF/2-nitrophenol[97] provided only elimination products **75** (Table 2, entries 3−5). Use of $(Bu_4N)Bu_3SnF_2$[98] promoted decomposition of **72** (Table 2, entry 6). Based on these observations, we recognized that basic fluoride reagents would not be effective in promoting the required deprotections. Consequently, we next investigated the use of inorganic fluoride sources (e.g., KHF_2) in mildly acidic reaction conditions, but glycoside **72** proved unreactive under these conditions (Table 2, entry 7). Use of more acidic conditions such as Dowex 50W-X4200 resin/MeOH or HF·Py lead to decomposition of the starting material (Table 2, entries 8 and 9).

Scheme 13 [a]

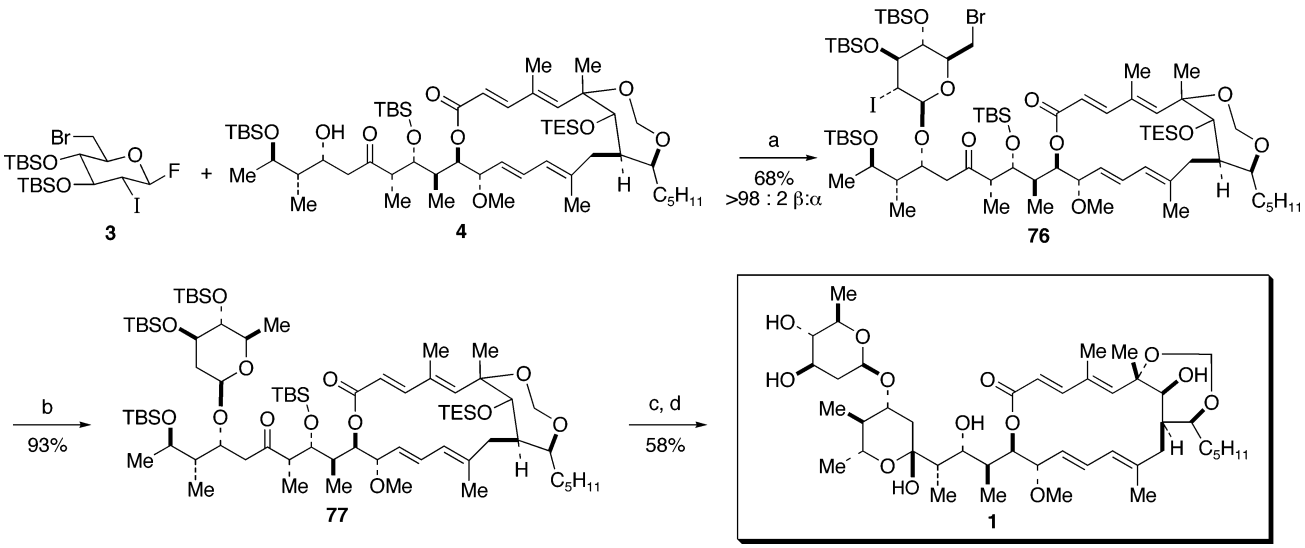


[a] Conditions: (a) AcOH, 1% HF·KF, THF, 33°C, 93 h; (b) Et_3B,O_2, Bu_3SnH, toluene, rt, 90%.

Given the data summarized in Table 2, it became clear that a neutral set of silyl deprotection conditions had the best chance of being effective. This realization lead to our consideration of Et_3N·3HF as a potential desilylation reagent.[99] While use of HF·Py had not been effective, presumably due to acid-catalyzed decomposition, it has been shown that Et_3N·3HF is a milder fluoride source, with a pH close to neutral.[100] Further, the addition of Et_3N to this reagent leads to formation of Et_3N·

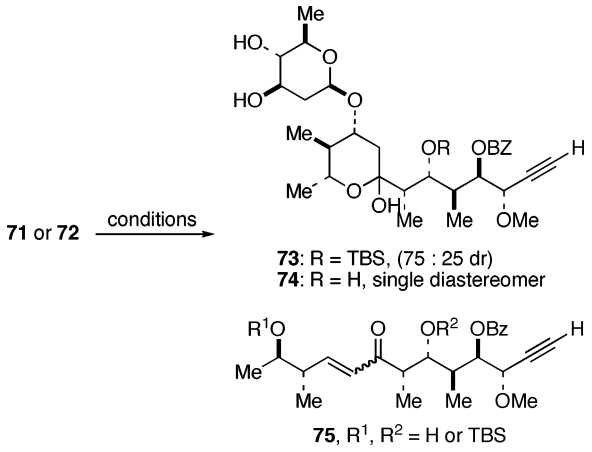
(96) Bennett, C. E. Ph.D. Thesis, Indiana University, Bloomington, IN, 2000.
(97) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732.
(98) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381.
(99) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.
(100) Saluzzo, C.; Alvernhe, G.; Anker, D. *J. Fluorine Chem.* **1990**, *47*.

Scheme 14 [a]



[a] Conditions: (a) $SnCl_2$, $AgClO_4$, Et_2O, 4 Å MS, −20 to −15 °C; (b) Bu_3SnH, Et_3B, O_2, 23 °C; (c) $Et_3N{\cdot}3HF$, Et_3N, CH_3CN/THF 1:1, 23 °C, 3 d; (d) $Et_3N{\cdot}3HF$, Et_3N, CH_3CN, 23 °C, 11 d.

Table 2. Desilylation of Glycosidated Model β-Hydroxy Ketones



entry	precursor	reagent	solvent	time	result
1	**71**	TASF	DMF	24 h	**75**
2	**71**	2,6-DCP[a] TASF	DMF	24 h	**75**
3	**72**	2-NP[b]	THF	5 min.	**75**
4	**72**	TBAF AcOH	THF	3.5 h	**75**
5	**72**	TBAF 2-NP	THF	24h	**75**
6	**72**	Bu_4N^+ $Bu_3SnF_2^-$	THF	24 h	dec[c]
7[d]	**72**	$KHF_{2(aq)}$ AcOH	THF	20 h	NR[e]
8	**72**	Dowex 50W-X4200	MeOH	24 h	dec[c]
9	**72**	HF·Py	THF	20 min	dec[c]
10	**72**	$Et_3N{\cdot}HF$ Et_3N	CH_3N	5 d	**73** (47%) **74** (39%)

[a] 2,6-DCP = 2,6-dichlorophenol. [b] 2-NP = 2-nitrophenol. [c] dec = decomposition. [d] Reaction stirred at 23 °C for 12 h and then at 50 °C for 6 h. [e] NR = no reaction, starting material recovered.

2HF and $Et_3N{\cdot}HF$.[101] Of the various forms, $Et_3N{\cdot}2HF$ is the most nucleophilic fluoride source and has been used to prepare alkyl fluorides via displacement reactions.[101] Therefore, we were gratified to find that exposure of glycoside **72** to in situ generated $Et_3N{\cdot}2HF$ in acetonitrile over 5 days indeed provided the desired product **74** in 39% yield (Table 2, entry 10). Interestingly, TBS ether **73** was also recovered from the reaction as a mixture of diastereomeric ketals in 47% yield.

Completion of the Total Synthesis of Formamicin. With a potential set of conditions to allow final desilylation in hand, our attention turned to the completion of the total synthesis of formamicin. In the event, glycosidation of aglycon **4** by donor **3** with $SnCl_2$ and $AgClO_4$[94] in Et_2O at −20 °C provided the desired glycoside **76** in 68% yield and with >98:2 β/α selectivity (Scheme 14).[51] Removal of the carbohydrate C(2′) and C(6′) halogen substituents with Bu_3SnH in toluene at 23 °C, via promotion with Et_3B/O_2,[85] proceeded in excellent yield to provide 2,6-dideoxy glycopyranoside **77**, the penultimate intermediate in the synthesis.

Interestingly, glycoside **77** was insoluble in acetonitrile, which required the use of THF as a cosolvent for our planned global desilylation reaction. After exposure of **77** to in situ generated $Et_3N{\cdot}2HF$[101] in 1:1 acetonitrile/THF, all but one of the TBS ether groups were removed (Scheme 11). Unfortunately, further exposure of this mono-TBS derivative[102] to these conditions failed to remove this lone remaining silyl group. We anticipated that this could be the result of the lower dielectric constant of the reaction medium,[99] originating from the introduction of the THF cosolvent. Therefore, the reaction was subjected to an aqueous workup[103] and the mono-TBS ether was treated with in situ generated $Et_3N{\cdot}2HF$ in acetonitrile. This reaction eventually proved successful, albeit slow (11 days), and provided

(101) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527.
(102) It is clear from the long reaction time (11 days) required to remove the last TBS ether from intermediate **77** that the environment around this group is highly sterically congested. Based on the recovery of **73** in the deprotection of model system **72**, we suspect that this intermediate is the C(17)−OTBS derivative of **1**. While we have not been able to unequivocally prove this assignment, support for this hypothesis is found in ^{1}H NMR analysis of the mono-TBS ether intermediate. This material exists as a mixture of diastereomeric ketals, just as **73**. In the ^{1}H NMR spectrum of the mono-TBS ether of **1**, a broad multiplet at 4.3 ppm is observed, rather than the doublet of doublets of doublets (ddd) at 4.2 ppm corresponding to the C(17)−H in **1**. Further, the sharp doublet at 4.9 ppm in **1**, originating from the C(17)−OH, is notably absent in this material. The C(17)−OH is involved in a characteristic hydrogen-bonding pattern in this natural product, and the absence of a resonance corresponding to C(17)−OH in the mono-TBS ether strongly points to this compound being the C(17)−OTBS derivative.

synthetic formamicin **1** in 58% overall yield for the two steps. The identity of synthetic **1** was confirmed by comparison to an authentic sample graciously provided by Igarashi and coworkers[33,34] using ^{1}H and ^{13}C NMR spectroscopy and TLC mobility in several solvent systems.

Summary. We have achieved the first total synthesis of formamicin (**1**) by a highly stereoselective sequence. Highlights of this work include development of both lactate aldol and chelate controlled carbonyl addition strategies to the C(1)−C(11) fragment **7** of the natural product, a Lewis acid promoted intramolecular transacetalation reaction to form the seven-membered formyl acetals **29** and **39**, an efficient and highly diastereoselective glycosidation of the protected aglycon **4** using fluoride donor **3**, and global desilylation of penultimate intermediate **77** using $Et_3N{\cdot}2HF$ to complete the total synthesis.

Acknowledgment. We thank the National Institutes of Health (GM 38436) for support of this research. We also acknowledge additional financial support in the form of a Lavoisier Fellowship from the Ministère Francais des Affaires Etrangères to N.B., an Abbott Graduate Fellowship to B.M.S., and an NIH postdoctoral fellowship (GM 20278) to N.A.P..

Supporting Information Available: Experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA048493L

(103) Following dilution of the reaction with Et_2O and washing with pH 7 buffer, the ethereal solution was dried over $KHCO_3/Na_2SO_4$ for 1 h prior to concentration on the rotary evaporator. Failure to use $KHCO_3$ resulted in decomposition of the material upon concentration. Presumably, this decomposition is promoted by residual HF. This protocol was first reported by Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639; see ref 14 therein.