Total Synthesis

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Enantioselective Synthesis of Putative Lipiarmycin Aglycon Related to Fidaxomicin/Tiacumicin B**

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Abstract: *An enantioselective synthesis of a putative lipiarmycin aglycon was accomplished and features: 1) Brown's enantioselective alkoxyallylboration and allylation of aldehydes, 2) chain elongation by iterative Horner–Wadsworth–Emmons olefination, 3) Evans' aldol reaction and 4) an enediene ring-closing metathesis. A neighboring-group-assisted chemoselective reductive desilylation was uncovered in this study and was instrumental to the realization of the present synthesis.*

Lipiarmycins A3 (**1**) and A4 (**2**; Figure 1) were isolated as a 3:1 mixture from *Actinoplanes deccanensis* ATCC 21983 by Parenti and co-workers in 1975.[1] The structure of **1** and **2** was elucidated in 1987,[2] and was followed by isolation of lipiarmycins B3 and B4 congeners a year after.[3] Other microbial metabolites structurally related to the lipiarmycins, such as clostomicins[4] and tiacumicins,[5] have subsequently been isolated from *Micromonospora echinospora* and *Dactylosporangium aurantiacum hamdenensis*, respectively. Tiacumicin B (**3**) acts as a RNA synthesis inhibitor by docking into two domains of the closed RNA polymerase, thus preventing its opening and activation. It has the same cure rate as vancomycin but with a lower relapse rate for the treatment of *Clostridium difficile* infection (CDI). In May 2011, the FDA approved tiacumicin B (fidaxomicin, Dificid®) as an alternative to the well-established metronidazole or vancomycin for the treatment of CDI.[6]

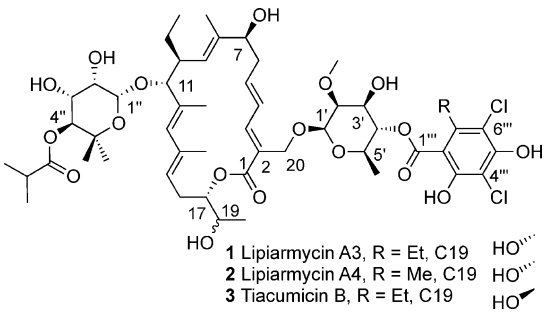
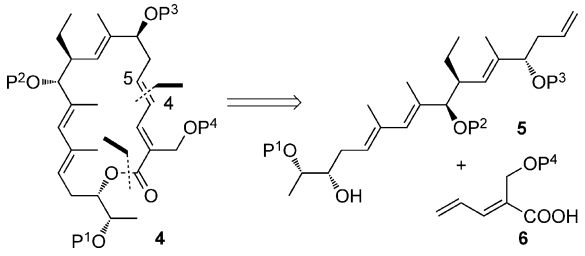


Figure 1. Structures of lipiarmycins and tiacumicin B.

To date, over 40 members of this family of macrolides have been isolated.[7] Structurally, these natural products share a common 18-membered macrolactone unit incorporating five stereogenic centers, two conjugated dienes, one trisubstituted double bond, and are O-glycosylated at C11 and C20. While the absolute configuration of the stereogenic centers in **3** was determined by single-crystal X-ray structural analysis, the stereochemistry of lipiarmycin aglycon remains ambiguous, especially with respect to the absolute configuration of C19. Shue and co-workers were among the first to assign the absolute configuration of lipiarmycin A4 (19*S*) as depicted in Figure 1.[8] However, a recent paper from the group of Serra has shown that lipiarmycin A3 and tiacumicin B (19*R*) might be identical.[9]

Given our interest in the chemistry and bioactivities of the lipiarmycins, we requested and received a sample of lipiarmycin A3 from Biosearch Italia. We started our research by detailed NMR studies of this natural product and deduced, independent of Optimer Pharmaceuticals' work, the stereochemistry of lipiarmycin A3 to be that shown in Figure 1.[10] A total synthesis based on this stereochemical assignment was subsequently initiated.[11,12] We describe herein our synthesis of presumed lipiarmycin aglycon.[13] The groups of Gademann and of Altmann have independently accomplished the synthesis of the tiacumycin B aglycon.[14]

Our retrosynthetic analysis of the lipiarmycin aglycon **4** is outlined in Scheme 1. Cleavage of both the ester function and the C4–C5 double bond would give the alcohol **5** and carboxylic acid **6**. In a forward sense, intermolecular cross-metathesis between **5** and **6** followed by macrolactonization



Scheme 1. Retrosynthesis of lipiarmycin aglycon.

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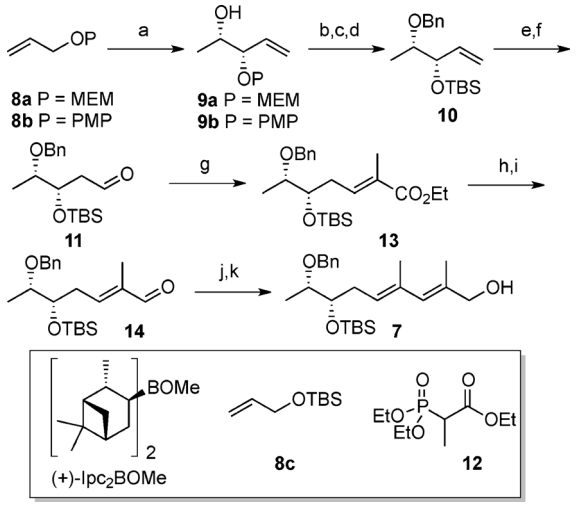
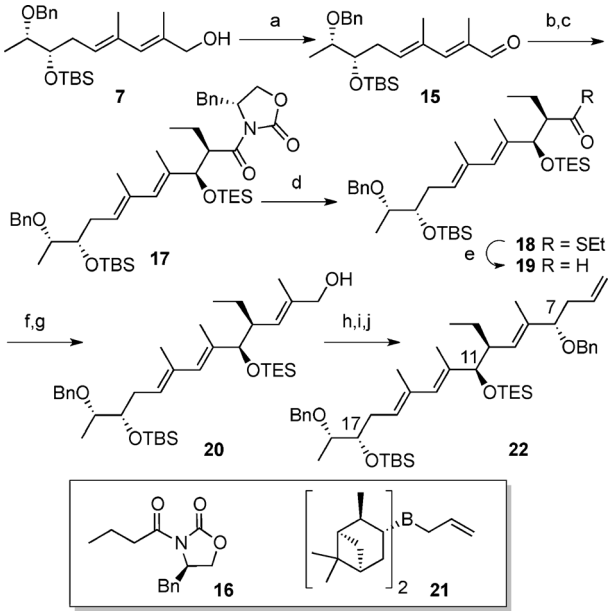


Scheme 2. a) *s*BuLi, THF, −78 °C, 30 min, then (+)-Ipc_2BOMe, −78 °C, 60 min, then $BF_3{\cdot}OEt_2$, −78 °C, then acetaldehyde, −78 °C, 3 h, then H_2O_2, NaOH, −78 °C to RT, 18 h, **9a** (74%, *ee* 93%); **9b** (80%, *ee* 92%); b) NaH, DMF, 0 °C, 1 h, then BnBr, 0 °C to RT, 18 h, 81%; c) CAN, MeCN, H_2O, 0 °C, 15 min, 81%; d) TBSCl, Imidazole, DMF, RT, 18 h, 90%; e) Cy_2BH, THF, 0 °C, 2 h, then H_2O_2, NaOH, 0 °C, 4 h, 73%; f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then NEt_3, −78 °C to RT, 1 h, 99%; g) **12**, NaH, THF, 0 °C, 20 min, then **11**, 0 °C, 2 h, 92%, *E*/*Z* = 7:1; h) DIBAL-H, Toluene, −78 °C, 1 h, 93%; i) MnO_2, THF, RT, 2 h; j) **12**, NaH, THF, 0 °C, 20 min, then **14**, 0 °C, 2 h, 78%, *E*/*Z* = 4:1; k) DIBAL-H, toluene, −78 °C, 1 h, 59%. CAN = cerium ammonium nitrate, Cy = cyclohexyl, DIBAL-H = diisobutylaluminium hydride, DMF = *N*,*N*dimethylformamide, DMSO = dimethylsulfoxide, Ipc = isopinocampheyl, MEM = 2-methoxyethoxymethyl, PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.



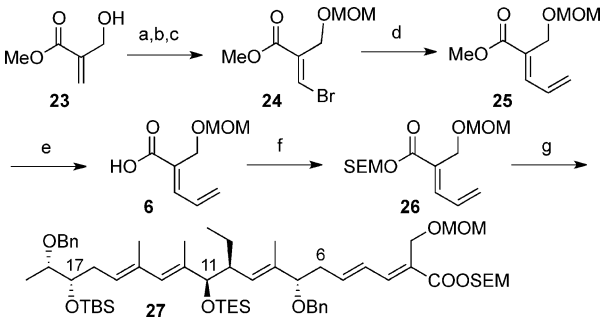
Scheme 3. a) MnO_2, THF, RT, 2 h; b) **16**, nBu_2BOTf, NEt_3, CH_2Cl_2, 0 °C, 30 min, then **15**, −78 °C to RT, then H_2O_2, MeOH, Buffer pH 7.0, 10 °C to RT, 1 h, 86% over 2 steps; c) TESCl, imidazole, DMF, 0 °C, 20 min, 73%; d) EtSH, *n*BuLi, THF, 0 °C, 5 min, then **17**, THF, RT, 10 min, 85%; e) DIBAL-H, CH_2Cl_2, −78 °C, 20 min; f) **12**, NaH, THF, 0 °C, 20 min, then **19**, 0 °C, 2 h, 70% over 2 steps, *E*/*Z* = 4:1; g) DIBAL-H, toluene, −78 °C, 1 h, 56%; h) MnO_2, THF, RT, 2 h; i) **21**, THF, −78 °C, 1 h, then H_2O_2, NaOH, −78 °C to RT, 3 h, 58%, *dr* = 3:1; j) NaH, nBu_4NI, DMF, 0 °C, 1 h, then BnBr, 0 °C to RT, 18 h, 40%. TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

or alternatively, esterification of the acid **6** by **5** and subsequent ring-closing metathesis of the resulting enediene,[15] could be envisaged for the formation of the 18-membered macrocycle.

We began our synthesis with the preparation of the diene **7** (Scheme 2). An enantioselective Brown alkoxyallylation of acetaldehyde by the allyl ether **8a** in the presence of (+)-Ipc_2BOMe[16] afforded the *syn*-diol **9a** as a single isolable diastereomer in 74% yield with 93% *ee*.[17] The absolute configuration of **9a** (2*S*, 3*S*) was determined according to Trost's method[18] and the observed enantioselectivity was in agreement with the literature precedent. Likewise, reaction of **8b** with acetaldehyde under identical reaction conditions provided **9b** (80%, *ee* 92%), which was converted into **10** by a sequence of known reactions. It is worthy to note that the TBS ether **8c** failed to react with acetaldehyde under standard reaction conditions. Hydroboration/oxidation of the olefin **10** followed by Swern oxidation of the resulting primary alcohol furnished the aldehyde **11** in 73% overall yield. Horner–Wadsworth–Emmons (HWE) olefination[19] of **11** with ethyl 2-(diethoxyphosphoryl)propanoate (**12**) provided the *trans*-olefin **13** as a major isomer and was transformed, upon reduction and oxidation, to the α,β-unsaturated aldehyde **14**. Applying the same HWE olefination/reduction sequence to **14** provided **7** without event.

Oxidation of **7** with MnO_2 afforded the unstable dienal **15** which was directly engaged in the Evans aldol reaction[20] with the oxazolidinone **16** to afford, after protection of the resulting hydroxy group as a TES ether, the compound **17** (Scheme 3). Reaction of **17** with in situ generated lithium ethanethiolate produced the thioester **18** which was reduced with DIBAL-H to the aldehyde **19**. Two-carbon homologation of **19** to the allylic alcohol **20** was accomplished by a standard HWE reaction/reduction sequence. Oxidation of the alcohol followed by addition of Brown's allylation reagent, (−)-Ipc_2BAllyl (**21**),[21] afforded, after O benzylation, the diastereomerically pure allyl ether **22**, a key tetraenic tetrol building block.

The macrolactonization strategy was initially examined for the synthesis of the lipiarmycin aglycon. Access to **6** and its elaboration to the cyclization precursor is detailed in Scheme 4. Methyl 2-(hydroxymethyl)acrylate (**23**)[22] was converted into the *E*-vinylbromide **24** through a sequence of O-MOM protection, bromination, and stereoseletive β elimination of HBr.[23] A Liebeskind-modified Stille coupling between **24** and tributylvinylstannane in the presence of copper thiophene carboxylate (CuTC) provided the diene **25** in 75% yield.[24] We noted that the Suzuki–Miyaura cross-coupling between **24** and either vinyl potassium trifluoroborate, vinylpinacolborane, or vinyl boroxine afforded the desired diene **25** in a low yield (20 to 40%). Saponification of the methyl ester was best realized using trimethyltin hydroxide as a nucleophile (dichloroethane, 80 °C)[25] to afford **6**, which was transformed into the 2-(trimethylsilyl)-ethoxymethyl (SEM) ester **26**[26] and was stable enough to be

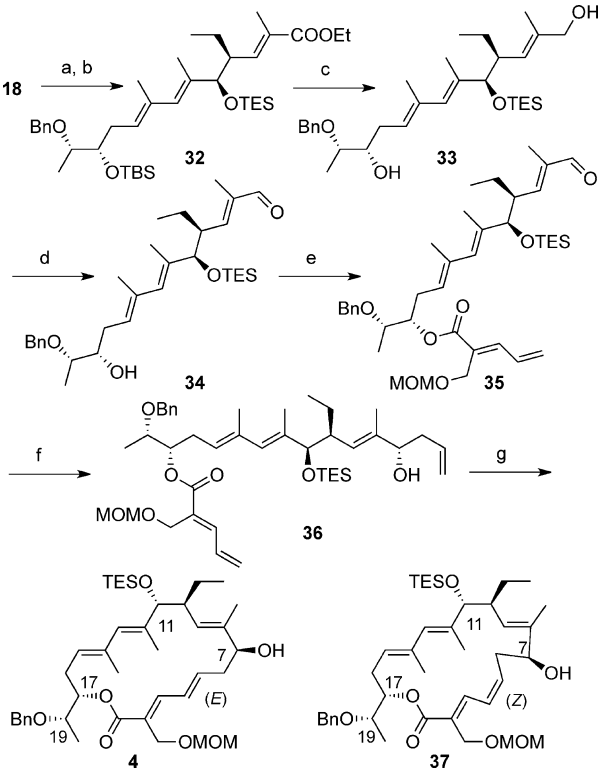


Scheme 4. a) MOMCl, iPr_2NEt, CH_2Cl_2, 0°C to RT, 18 h, 26%; b) Br_2, CCl_4, Reflux, 30 min, 54%; c) TBAF, HMPA, 0°C to RT, 1 h, 73%; d) tributylvinylstannane, CuTC, NMP, 0°C, 10 min, 57%; e) Me_3SnOH, 1,2-DCE, 80°C, 5 days, 31%; f) SEMCl, Cs_2CO_3, DMF, RT, 18 h, 87%; g) **22**, Hoveyda-Grubbs II (25 mol%), toluene, 100°C, M.W., 15 min, 38%; DCE = 1,2-dichloroethane, HMPA = hexamethylphosphoramide, MOM = methoxymethyl, M.W. = microwave, NMP = *N*-methylpyrrolidinone, SEM = tri(methylsilyl)ethoxymethyl, TBAF = tetrabutylammonium fluoride, TC = thiophene carboxylate.

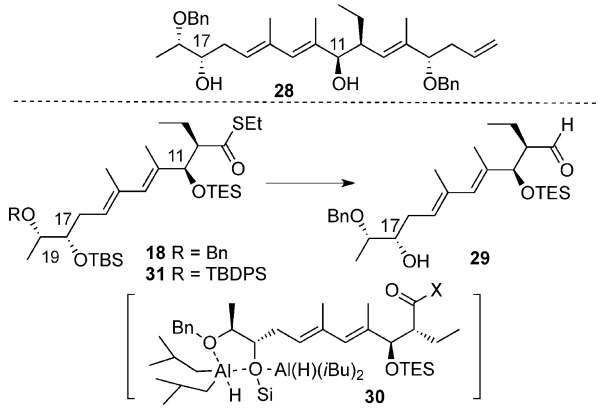
purified by chromatography on silica gel. Cross-metathesis between **22** and **26** was problematic, thus affording **27** in only 38% yield in the presence of the Hoveyda–Grubbs II catalyst.[27] Unfortunately, all trials to selectively remove the C17–OTBS and C1–OSEM ester protective groups led to a complex reaction mixture or degradation of the starting material under forcing conditions. The instability of diene units as well as the tendency of **27** to undergo dehydration to the conjugated polyene could account for the experimental observation. Indeed because of the presence of the C1 ester group, the H on C6 is quite acidic and is prone to induce a cascade dehydration leading to highly unstable polyenes.

The failure encountered in the deprotection of **27** prompted us to examine an alternative esterification/RCM strategy (Scheme 5). Acylation of the diol **28** derived from **22** turned out to be nonregioselective even with substoichiometric amounts of the acylation agent. Therefore, access to a substrate with a free C17 hydroxy group was needed. During the optimization process for the reduction of **18** with DIBAL-H, we isolated a variable amount of the hydroxy aldehyde **29** in which the C17–OTBS ether was chemoselectively removed. We hypothesized that formation of the five-membered aluminum chelate **30** is responsible for this unexpected result[28] based on the fact that the compound **31** failed to undergo the regioselective O desilylation.

This observation allowed development of a successful synthesis of the putative lipiarmycin aglycon **4** (Scheme 6).



Scheme 6. a) DIBAL-H (1.0 M in hexane, 2 equiv), toluene, −78°C, 20 min; b) **12**, NaH, THF, 0°C, 2 h, then crude aldehyde **19**, 0°C, 2 h, 65% over two steps, $E/Z = 4:1$; c) DIBAL-H (1.0 M in hexane, 5 equiv), CH_2Cl_2, −78°C, 1 h, 71%; d) MnO_2, THF, RT, 2 h; e) **6**, 1,3,5-trichlorobenzoyl chloride, Et_3N, toluene, RT, 1 h, then **34**, DMAP, RT, 4 h, 53% from **33**; f) **21**, THF, −78°C, 1 h, then H_2O_2, NaOH, −78°C to RT, 3 h, 42%; g) Grubbs II (0.2 equiv), toluene, 100°C, 43%, $E/Z = 2:1$. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.



Scheme 5. Selective deprotection under reductive conditions: a neighboring-group effect.

Reduction of **18** with DIBAL-H (1.0 M in hexane) followed by a HWE reaction afforded the triene **32**. After a rapid filtration of the crude reaction mixture, a dichloromethane solution of **32** was treated with an excess of DIBAL-H (1.0 M solution in hexane, 5 equiv, −78°C) to afford the diol **33** in which the C17–OTBS ether was chemoselectively removed. Chemoselective oxidation of allylic alcohol in the presence of the secondary alcohol afforded the hydroxy aldehyde **34** which was esterified with **6** under Yamaguchi conditions to afford the aldehyde **35**.[29] Allylation of **35** with **21** afforded the desired diastereomer **36** in a 42% yield. The final RCM of ene-diene afforded two separable macrolactones, **4** and **37**, in yields of 28 and 15%, respectively.[30] Detailed NOE studies allowed us to conclude that the major isomer has the desired *E* geometry of the newly formed double bond (see the Supporting Information).

In summary, we developed an enantioselective synthesis of putative lipiarmycin aglycon featuring a key RCM for the closure of the 18-membered macrocycle. While iterative HWE reaction was used for chain elongation, the stereogenic centers of the macrolide were installed and controlled by Brown's alkoxyallylboration, allylation, and an Evans aldol reaction. A neighboring-group-assisted chemoselective reductive O-desilylation process was uncovered and was instrumental in leading to the completion of our synthesis.

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Keywords: macrocycles · metathesis · natural products · protecting groups · total synthesis

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Communications

Total Synthesis

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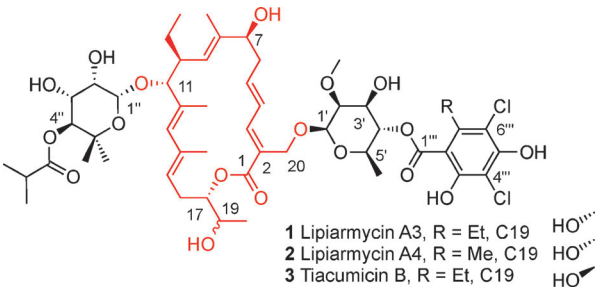
Enantioselective Synthesis of Putative Lipiarmycin Aglycon Related to Fidaxomicin/Tiacumicin B



Chain gang: The synthesis of the title compound is reported. The ene-diene ring-closing metathesis was used for the formation of the 18-membered macrolactone and the stereogenic centers of the molecule were installed by Brown's alkoxyallylboration, allylation, and an Evans aldol reaction, while iterative Horner–Wadsworth–Emmons reactions were used for chain elongation.