Natural Product Synthesis

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Total Synthesis of the Tiacumicin B (Lipiarmycin A3/Fidaxomicin) Aglycone**

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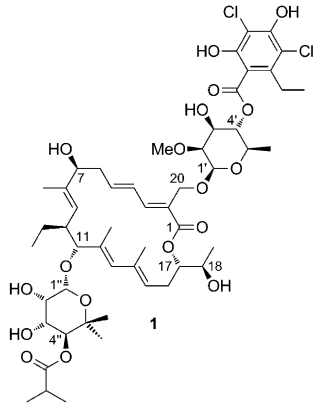
Abstract: *Tiacumicin B (lipiarmycin A3, fidaxomicin) is an atypical macrolide antibiotic which is used for the treatment of Clostridium difficile infections. Tiacumicin B is also a potent inhibitor of Mycobacterium tuberculosis, but due to its limited oral bioavailability is unsuitable for systemic therapy. To provide a basis for structure–activity studies that might eventually lead to improved variants of tiacumicin B, we have developed an efficient approach to the synthesis of the tiacumicin B aglycone. The synthesis features a high-yielding intramolecular Suzuki cross-coupling reaction to effect macrocyclic ring closure. Key steps in the synthesis of the macrocyclization precursor were a highly selective, one-pot Corey–Peterson olefination and an ene–diene cross-metathesis reaction. Depending on the reaction conditions, the final deprotection delivered either the fully deprotected tiacumicin B aglycone or partially protected versions thereof.*

In 1987 researchers at Abbott Laboratories described the isolation of the glycosylated macrolide tiacumicin B (**1**) as the major antibacterial constituent of the soil bacterium *Dactylosporangium aurantiacum*.[1,2] The compound was found to be identical[1b] to lipiarmycin, which had already been isolated in 1975 from *Actinoplanes deccanensis*,[3] and to clostomicin B1, isolated from *Micromonospora echinospora* in 1986.[4] The original preparation of lipiarmycin[3] was later discovered to be a ca. 3:1 mixture of two closely related macrolides, lipiarmycin A3 and lipiarmycin A4, whose gross chemical structures were determined in 1987.[5] The complete relative and absolute configuration of **1** (from *Dactylosporangium aurantiacum*) was elucidated in 2005 by X-ray crystallographic analysis;[6] importantly, most recently, **1** has been shown to be identical to lipiarmycin A3.[7]

The structure of tiacumicin B (**1**) features an 18-membered macrolactone core with four chiral centers and a high degree of unsaturation; an additional, hydroxy-bearing stereogenic center is present in the short side chain attached to C17. The aglycone core is connected via glycosidic linkages to 4-*O*-isobutyryl-5-methyl-β-D-rhamnose (at C11) and to 2-*O*-methyl-β-D-rhamnose (at C20), with the latter being esterified at C4 with dichlorohomoorsellinic acid.



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Tiacumicin B (**1**) is an inhibitor of bacterial RNA polymerase[8] and it exhibits significant antibacterial activity against a range of Gram-positive organisms[9] and also against *Mycobacterium tuberculosis*.[10] At the same time, the compound is not susceptible to cross-resistance with rifamycin-type antibiotics,[10] which were the only class of bacterial RNA polymerase inhibitors of clinical significance before 2011 (vide infra). Notably, **1** shows only minimal oral bioavailability,[11] which limits its utility for the treatment of systemic infections, but renders it highly useful for the elimination of pathogens confined to the gastrointestinal tract. In 2011, tiacumicin B (**1**), under the generic name fidaxomicin (trade names Dificid (U.S.) and Dificlir (Europe)), was approved for the treatment of infections with the opportunistic pathogen *Clostridium difficile*, which is the most frequent cause of nosocomial diarrhea infections in the developed world.[12]

Rather surprisingly, despite their intriguing structures and biological profiles, no total synthesis of any member of the tiacumicin/lipiarmycin/clostomicin family (or the corresponding aglycones) has been reported in the literature to date. In the context of our work on new drugs against tuberculosis,[13] we have thus embarked on the total synthesis of the tiacumicin B aglycone (**2**; Scheme 1), in order to provide a basis for structure–activity relationship (SAR) studies.[14] Ultimately, this work aims to identify tiacumicin B analogues with improved biopharmaceutical properties. Alternative approaches to the synthesis of the tiacumicin B aglycone (**2**) and its 18*S* isomer are described in two concurrent papers in this issue by the groups of Gademann and Zhu, respectively.[32]

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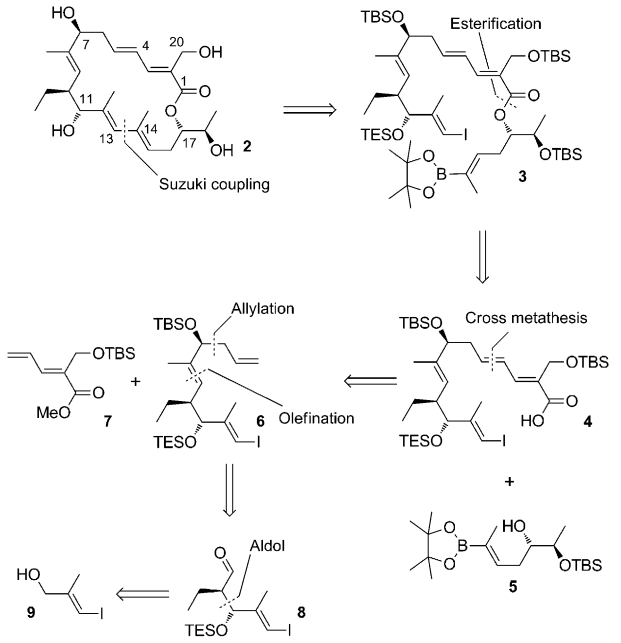
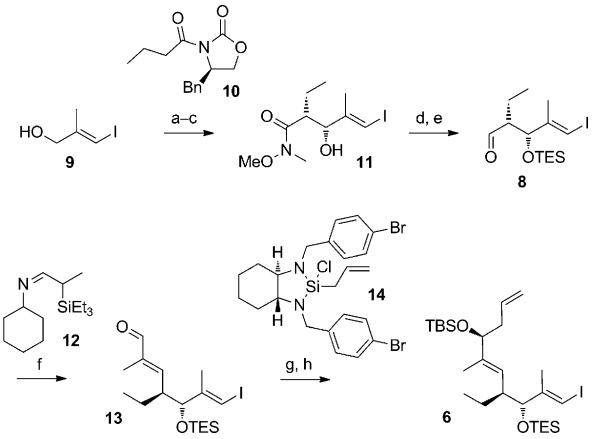


Scheme 1. Retrosynthesis of the tiacumicin B aglycone (**2**). TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.



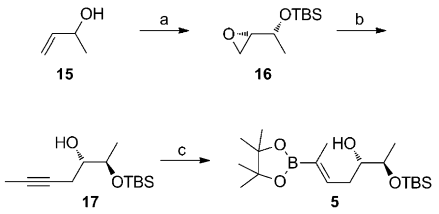
Scheme 2. a) MnO_2, 3 Å molecular sieves, CH_2Cl_2, RT, 75 min; b) **10**, Bu_2BOTf, NEt_3, CH_2Cl_2, −78 °C, 2.5 h; then 0 °C, 1.5 h; then pH 7 buffer, MeOH, H_2O_2, 0 °C, 1 h; c) MeONHMe·HCl, $AlMe_3$, THF, 0 °C, 2 h, 53 % (three steps); d) TESCl, imidazole, CH_2Cl_2, RT, 30 min, 94 %; e) DIBAL-H, THF, −30 °C, 1 h; then −20 °C, 1 h, 94 %; f) **12**, *s*BuLi, THF, −20 °C, 2 h; then PhSH, −20 °C, 2 h; then sat. aq. NaH_2PO_4, RT, 4 h, *E*/*Z* 20:1, 81 % (ca. 95 % pure); g) **14**, $Sc(OTf)_3$, CH_2Cl_2, −35 °C to −20 °C, 30 min; then −20 °C, 2.5 h; then 1 M HCl, RT, 7 min, 83 %, d.r. > 20:1; h) TBSCl, imidazole, CH_2Cl_2, RT, 22 h, 93 %. OTf = trifluoromethanesulfonate, DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran.

As illustrated in Scheme 1, one of the central elements of our projected synthesis of **2** was the use of an intramolecular Suzuki cross-coupling reaction to effect macrocyclic ring closure. The requisite macrocyclization precursor **3** could be disconnected into acid **4** and alcohol **5**; the former was to be obtained by ene–diene cross-metathesis between olefin **6** and diene **7**,[15] followed by ester saponification. While olefin–olefin cross-metathesis has found numerous applications in organic synthesis, reactions involving conjugated dienes such as **7** have been investigated only scarcely.[16] The terminal olefin **6** was envisioned to be synthesized from the known alcohol **9**[17] by a sequence of oxidation, stereoselective aldol reaction, olefination, and stereoselective allylation. Finally, protecting groups were chosen such as to allow for stepwise selective deprotection of the C11 and C20 hydroxy groups, in order to enable subsequent independent derivatization at these positions for analogue synthesis (or the synthesis of the natural product **1**).

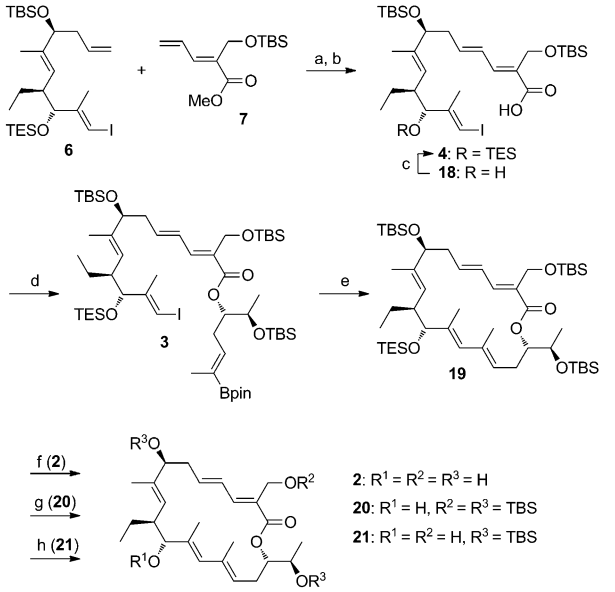
Based on the above retrosynthetic considerations, the synthesis commenced with the MnO_2-mediated allylic oxidation of **9** (Scheme 2). The resulting volatile aldehyde was not isolated, but the reaction mixture was filtered through celite and the concentrated filtrate was treated directly with the boron enolate of **10**;[18] this protocol gave the desired *syn*-aldol product with excellent diastereoselectivity (d.r. > 20:1). Separation of the aldol product from unreacted **10** proved to be difficult and thus was not attempted for multigram-scale reactions. Rather, the mixture, after aqueous workup and filtration through silica, was treated with $AlMe_3$/MeONHMe·HCl to provide Weinreb amide **11** in 53 % overall yield for the three-step sequence from **9**. The absolute configuration of **11** was secured by X-ray crystallography (see the Supporting Information for details).[19] TES protection of the secondary hydroxy group followed by reduction of the Weinreb amide functionality with DIBAL-H then furnished aldehyde **8**. Aldehyde **8** was then transformed into enal **13** by a newly developed variant of the Corey–Peterson olefination reaction,[20] which employed thiophenol (rather than the commonly used trifluoroacetic acid)[21] to isomerize the *E*/*Z* mixture of aldimines formed upon addition of the anion of α-silylimine **12** to aldehyde **8**. Treatment of the aldimine mixture (*E*/*Z* ca. 1:3) with thiophenol in situ induced rapid *Z* to *E* isomerization, yielding imine mixtures with *E*/*Z* ratios of between 15:1 and 22:1 within two hours;[21] hydrolysis of the imine moiety then afforded enal **13** in 81 % yield and 95 % purity. Allylation of **13** with Leighton's strained silacycle **14**[22] in the presence of $Sc(OTf)_3$[23] set the C7 stereocenter (tiacumicin numbering) with excellent selectivity (d.r. > 20:1) and in high yield (83 %).[24] TBS protection of the secondary hydroxy group then furnished the desired building block **6**.

The synthesis of building block **5** departed from racemic but-3-en-2-ol (**15**), which was subjected to Sharpless kinetic resolution, affording, after in situ protection of the hydroxy group, **16** in 21 % yield (compare to a maximum yield of 45 %) (Scheme 3).[25] The epoxide ring in **16** was then smoothly opened with the anion of propyne to provide **17** in 75 % yield. Cu^I-catalyzed formal hydroboration[26,27] then afforded *Z*-vinyl boronic ester **5** with superb regio- (> 20:1) and stereoselectivity (*Z*/*E* > 20:1) in 79 % yield.

With all fragments in hand, the assembly of the tiacumicin B aglycone (**2**) was investigated, with the initial focus on the crucial cross-metathesis step (Scheme 4). These experiments revealed a pronounced tendency of diene **7** towards rapid homodimerization, regardless of the catalyst used (Grubbs I, II, and III; Hoveyda–Grubbs I and II, Piers–Grubbs),[28] solvent (toluene, CH_2Cl_2, Et_2O, EtOAc, THF,



Scheme 3. a) Ti(O*i*Pr)$_4$, (−)-DIPT, *t*BuOOH (0.45 equiv), 3 Å molecular sieves, CH_2Cl_2, −20 °C, 39 h; then TBSCl, imidazole, CH_2Cl_2, −20 °C to RT; then RT, 16 h, 21%; b) *n*BuLi, propyne, $BF_3{\cdot}OEt_2$, THF, −78 °C, 3.5 h, 75%, 18% recovered **16**; c) bis(pinacolato)diboron, CuCl (5 mol%), KO*t*Bu (20 mol%), PPh_3 (6 mol%), THF/MeOH, RT, 3.5 h, 79%. (−)-DIPT = (−)-diisopropyl D-tartrate.



Scheme 4. a) Hoveyda–Grubbs II (15 mol%), EtOAc, RT, 3.5 h, 56%, *E*/*Z* 6.7:1 at C4–C5, 27% recovered **6**; b) LiOH, *t*BuOH/H_2O 3:1, 33 °C, 48 h, 69% (**4**), 16% (**18**); c) 1. TESCl, imidazole, CH_2Cl_2, RT, 14 h; 2. K_2CO_3, MeOH, RT, 10 min, 84% (two steps); d) **5**, 2,4,6-$Cl_3H_2C_6COCl$, NEt_3, DMAP, toluene, RT, 5.5 h, 81%; e) [Pd(PPh_3)$_4$] (20 mol%), TlOEt, THF/H_2O 3:1, RT, 25 min, 73%; f) $NEt_3{\cdot}3$ HF, CH_3CN, 0 °C to RT, 1 h; then RT, 8 h; then 50 °C, 86 h, 47% after HPLC purification; g) $NEt_3{\cdot}3$ HF, CH_3CN/THF 7:3, −15 °C, 4 h; then −25 °C, 15 h; then −15 °C, 7 h, 70% (**20**), 22% (**19**); h) $NEt_3{\cdot}3$ HF, CH_3CN/THF 6:4, −15 °C to 5 °C, 2 h; then 5 °C, 5 h; then 15 °C, 27 h, 54%. Bpin = pinacolatoboron, DMAP = 4-dimethylaminopyridine.

dioxane, and C_6F_6 were investigated), and temperature (0 °C to 80 °C). In addition, rapid catalyst deactivation was noticed in all cases. In general, second-generation Grubbs and Hoveyda–Grubbs catalysts gave better conversions and higher *E*/*Z* ratios for the newly formed C4–C5 double bond than first- and third-generation catalysts. Best results were obtained when separate solutions of **7** and Hoveyda–Grubbs II catalyst in EtOAc were added simultaneously to a solution of **6** in EtOAc at room temperature (syringe pump addition). Following this protocol, the desired cross-metathesis product could be isolated in 56% yield as an inseparable 6.7:1 mixture of *E*/*Z* isomers at C4–C5; at the same time, 27% of the more valuable fragment **6** could be re-isolated.

Careful saponification of the ester group in the metathesis product with LiOH in *t*BuOH/H_2O at slightly elevated temperature (33 °C) afforded acid **4** in 69% yield together with some TES-deprotected material (**18**); the latter could be readily converted into **4** by reaction with an excess of TESCl.[31] Esterification of **4** with alcohol **5** (Scheme 4) using a Yamaguchi protocol[29] then provided **3**, as the requisite precursor for the projected Suzuki macrocyclization. Ring closure was effected by treating **3** with [Pd(PPh_3)$_4$] followed by TlOEt in a mixture of THF and water.[30] Remarkably, under these conditions the reaction was usually complete in less than 30 min at room temperature and furnished the desired macrocycle **19** in 73% yield as a 9.5:1 mixture of *E*/*Z* isomers at C4–C5.[31]

While **19** was not crystalline, a differently protected version of the compound (i.e. **22**, Figure 1) afforded crystals suitable for X-ray analysis,[19] which confirmed the correct configurations of all stereocenters and double bonds (for details see the Supporting Information). Importantly, **22** was

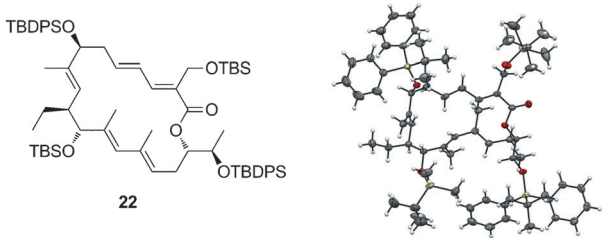


Figure 1. Structural formula and ORTEP representation of **22**; thermal ellipsoids drawn at 50% probability. Disorders were omitted (see the Supporting Information for details). TBDPS = *tert*-butyldiphenylsilyl.

obtained from **9** by the same route as **19** (except for the introduction of protecting groups). Global desilylation of **19** was best achieved with $NEt_3{\cdot}3$ HF, which provided **2** in 47% yield after purification by preparative HPLC (Scheme 4).[31] When the reaction temperature was lowered from 55 °C to 15 °C or −15 °C, it was possible to use the same reagent to remove the secondary TES group (→**20**) with reasonable selectivity, or selectively cleave the TES ether and the primary TBS ether simultaneously (→**21**), thus generating substrates suitable for further functionalization, including the synthesis of tiacumicin B (**1**).

In conclusion, we have developed an efficient synthesis of the tiacumicin B aglycone (**2**). The synthesis comprises 12 linear steps from alcohol **9** to the fully protected aglycone **19**. Key steps are a modified Corey–Peterson olefination, which allowed for the one-pot formation of *E*-α-methyl α,β-unsaturated aldehyde **13**, a cross-metathesis reaction between **6** and **7**, and a highly efficient intramolecular TlOEt-promoted Suzuki coupling as the macrocyclization step. Based on the chemistry presented in this paper, current work in our laboratory focuses on the synthesis of tiacumicin analogues and their biological evaluation.

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