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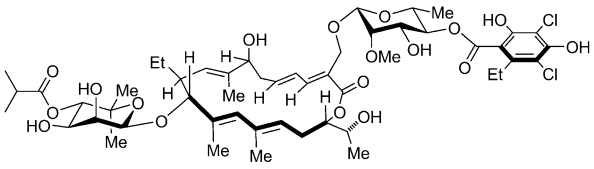
Total Synthesis of the Protected Aglycon of Fidaxomicin (Tiacumicin B, Lipiarmycin A3)**

*Hideki Miyatake-Ondozabal, Elias Kaufmann, and Karl Gademann**

Abstract: *Fidaxomicin, also known as tiacumicin B or lipiarmycin A3, is a novel macrocyclic antibiotic that is used in hospitals for the treatment of Clostridium difficile infections. This natural product has also been shown to have excellent bactericidal activity against multidrug-resistant Mycobacterium tuberculosis. In spite of its attractive biological activity, no total synthesis has been reported to date. The enantioselective synthesis of the central 18-membered macrolactone is reported herein. The key reactions include ring-closing metathesis between a terminal olefin and a dienoate moiety for macrocyclization, a vinylogous Mukaiyama aldol reaction, and a Stille coupling reaction of sterically demanding substrates. The retrosynthesis involves three medium-sized fragments, thus leading to a flexible yet convergent synthetic route.*

Among all the treatable diseases, tuberculosis (TB) remains a major public health concern worldwide.[1] Approximately nine million new cases of TB and an estimated two million deaths occur each year.[2] Current therapeutic options, such as the use of the frontline drugs rifampicin and isoniazid, have become limited owing to the spread of resistant forms of the bacterium.[3] Hence, the development of new pharmaceuticals against *Mycobacterium tuberculosis* has become an urgent task in medical research. In this context, we became interested in fidaxomicin (**1**, tiacumicin B, lipiarmycin A3),[4]



fidaxomicin (**1**, tiacumicin B, lipiarmycin A3)

which is an inhibitor of bacterial RNA polymerase and shows promising antibacterial activity against TB.[1] The molecule is also structurally attractive, owning a complex 18-membered aglycon fragment with multiple stereogenic centers and two glycosidic linkages where the eastern glycoside carries a fully substituted dichlororesorcinol unit. Unfortunately, the low bioavailability and the instability of the compound under acidic conditions make it unsuitable for use as a therapeutic for TB.[5] Structural modification, by either semi- or total synthesis, could therefore be crucial to improve its pharmacokinetic profile.

Currently, fidaxomicin is used in the clinic for the treatment of a different disease, namely *Clostridium difficile* infections, and was introduced to the market by Optimer pharmaceuticals in 2011.[6] Fidaxomicin has demonstrated similar clinical cure rates compared to vancomycin, however it is considered to be superior owing to its favorable adverse effect profile and decreased rates of disease recurrence. Given its proven potential as a pharmaceutical, we started to investigate an efficient and convergent total synthesis of fidaxomicin (**1**) to allow access to structurally diverse analogues with appropriate pharmacokinetics for the treatment of TB. It is remarkable that no total synthesis has been reported since its first isolation through fermentation of *Actinoplanes deccanensis* in 1975, despite its clinical use as a pharmaceutical agent.[7] To date, synthetic studies of the core aglycon have been documented in a PhD thesis,[8] and studies on the carbohydrate[9,10] and resorcinol[11] parts have been reported. Independent and concomitant syntheses of the lipiarmycin A3 macrolactone and a putative lipiarmycin aglycon have been reported by the groups of Altmann and Zhu, respectively.[12]

Herein, we report the successful synthesis of the central aglycon of fidaxomicin (**1**) through an approach featuring a vinylogous Mukaiyama aldol reaction (VMAR), a Stille coupling reaction, Yamaguchi esterification, and a ring-closing metathesis (RCM). We established a relatively short and highly convergent synthetic route to the macrocycle **2**, and our retrosynthetic analysis led to three main building blocks: vinyl iodide **3**, vinyl stannane **4**, and dienoic acid **5** (Scheme 1).

The synthesis started with the preparation of silyl ketene N,O-acetal **7** through γ-deprotonation and O-*tert*-butyldimethylsilylation of the known building block **6** (Scheme 2).[13] Subsequently, *anti*-selective VMAR[14] was performed between **7** and freshly prepared (*E*)-3-iodo-2-methylacrylaldehyde in the presence of $TiCl_4$ as a Lewis acid. In searching for the best reaction conditions, we found that a higher reaction concentration led to the best yield and diastereoselectivity (47%, d.r. > 20:1, 35% recovery of desilylated starting material **6**). To our knowledge, this transformation represents the first example of a VMAR, developed by Kobayashi et al.,[14] in which a different substituent (an ethyl

[*] Dr. H. Miyatake-Ondozabal, E. Kaufmann, Prof. Dr. K. Gademann
Department of Chemistry, University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
E-mail: karl.gademann@unibas.ch
Homepage: http://www.chemie.unibas.ch/~gademann

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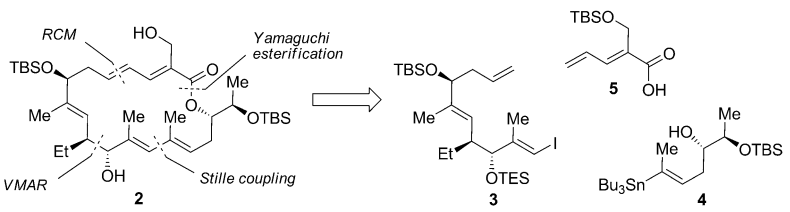
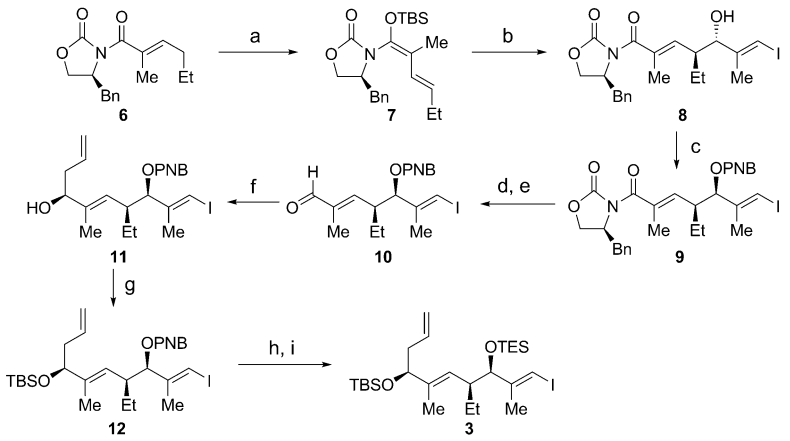


Scheme 1. Retrosynthetic analysis for the target macrolactone **2**.



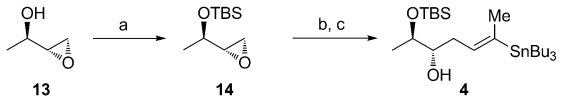
Scheme 2. Synthesis of vinyl iodide fragment **3**. a) NaHMDS, THF, −78 °C; then TBSCl, 97%; b) (*E*)-3-iodo-2-methylacrylaldehyde, $TiCl_4$, CH_2Cl_2, −78 °C to −30 °C, 47%, d.r. > 20:1; c) *para*-nitrobenzoic acid, DEAD, PPh_3, THF, 0 °C, 78%; d) $NaBH_4$, THF/H_2O; e) MnO_2, CH_2Cl_2, 76% (2 steps); f) (−)-Ipc_2B(allyl), Et_2O, −78 °C; then aq. $NaBO_3$, 70%, d.r. = 20:1; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 93%; h) K_2CO_3, $MeOH/H_2O$; i) TESOTf, 2,6-lutidine, CH_2Cl_2, 95% (2 steps). DEAD = diethyl azodicarboxylate, HMDS = hexamethyldisilazane, Ipc = isopinocampheyl, PNB = *para*-nitrobenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, THF = tetrahydrofuran.

group in our case) has been utilized as opposed to the standard methyl group. In order to obtain the desired *syn*-configured product, a Mitsunobu inversion was carried out to give ester **9** in 78% yield.[15] The selective cleavage of Evans auxiliary[16a] over the PNB ester was achieved under reducing conditions,[16b] and subsequent allylic oxidation with MnO_2 gave the α,β-unsaturated aldehyde **10** in 76% yield over two steps. The absolute configuration of the product was unambiguously confirmed by single crystal X-ray crystallographic analysis of its vinyl bromide derivative. The next step involved a diastereoselective Brown allylation of aldehyde **10** with (−)-allyl-diisopinocampheylborane.[17] A high diastereoselectivity of 20:1 was observed, along with an acceptable yield of 70%. TBS protection of the allylic alcohol **11** furnished silyl ether **12** (93%). Subsequent exchange of the protecting groups from benzoyl esters to silyl ethers (95% over two steps) turned out to be essential to successfully accomplishing the cross-coupling reaction.

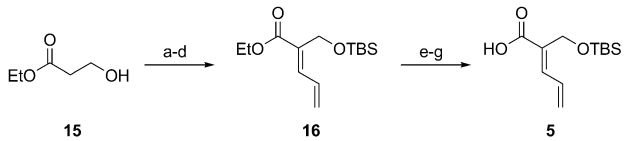
The southern building block of the macrolactone was prepared in three synthetic steps (Scheme 3). The synthesis began with silyl etherification[18] of the known chiral epoxy alcohol **13** (93%, e.r. > 99:1), which is accessible through kinetic resolution of 3-buten-2-ol by using Sharpless epoxidation.[19] Regioselective epoxide opening[20] with propynyllithium and boron trifluoride diethyl etherate was followed by Pd-catalyzed hydrostannylation to give the secondary alcohol **4** in 46% yield over two steps. During the course of hydrostannylation, formation of the undesired regioisomer could not be suppressed, thus leading to only moderate yield. Other approaches such as hydrozirconation[21] and stannyl cupration[22] gave complex mixtures of products.

The final building block **5** constitutes the eastern part of the macrolactone and incorporates the dienoic acid moiety (Scheme 4). First, commercially available ethyl 3-hydroxypropanoate (**15**) was treated with excess of lithium diisopropylamide and reacted with acrolein to furnish the corresponding aldol product. Next, monoselective *tert*-butyldimethylsilylation mediated by dimethyltin dichloride[23] was followed by acetylation and base-induced E_{1cb} elimination to give dienoate **16** in 54% yield over four steps (d.r. = 5.5:1). Finally, formal hydrolysis (DIBAH reduction, allylic and Lindgren–Pinnick oxidations) of ester **16** was executed to give the corresponding carboxylic acid **5** in 70% yield over three steps. It is worth mentioning that the standard hydrolysis conditions with either lithium hydroxide or sodium hydroxide led to desilylation as a major side reaction.

With the three building blocks **3**, **4**, and **5** in hand, we focused our attention on the Stille coupling step. As anticipated, this transformation was experimentally challenging owing to the sterically damanding nature of both the vinyl iodide and stannane fragments. After screening several sets of reaction conditions, we identified

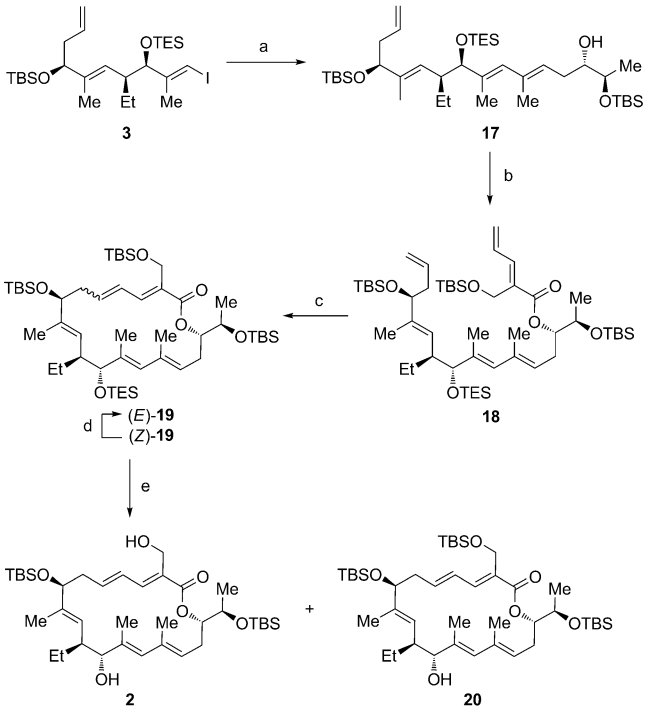


Scheme 3. Synthesis of vinyl stannane fragment **4**. a) TBSCl, Imid, CH_2Cl_2, 93%; b) propyne, *n*BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C to 0 °C, 90%; c) $Pd(OAc)_2$, PCy_3, Bu_3SnH, hexane, 51%. Imid = imidazole, Cy = cyclohexyl.



Scheme 4. Synthesis of dienoic acid fragment **5**. a) LDA (3.5 equiv), THF, −78 °C; then acrolein, −78 °C; b) Me_2SnCl_2 (10 mol%), TBSCl, Et_3N, 75% (2 steps); c) Ac_2O, Et_3N, DMAP, CH_2Cl_2; d) DBU, CH_2Cl_2, 72% (2 steps), *E*:*Z* = 5.5:1; e) DIBAH, CH_2Cl_2, −10 °C; f) MnO_2, CH_2Cl_2; g) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, 70% (3 steps). LDA = lithium diisopropylamide, DBU = 1,8-diazabicycloundec-7-ene, DIBAH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine.

the optimal conditions as a combination of copper thiophene-2-carboxylate (CuTC)[24] and $[Pd(PPh_3)_4]$ in the presence of tetrabutylammonium diphenylphosphonate salt.[25] These conditions give the diene **17** in very high yield of 77% (Scheme 5). The only significant side reaction was self-



Scheme 5. Synthesis of bis(silyl)-protected aglycon **2**. a) **4**, CuTC, [Pd-$(PPh_3)_4$], $[Bu_4N]^+[Ph_2PO_2]^-$, DMF, 77%; b) **5**, $Cl_3C_6H_2COCl$, Et_3N, DMAP, PhMe, 86%; c) Grubbs cat. II (15 mol%), PhMe, 40°C (microwave irradiation), 10 min, E/Z = 2:3; then 100°C, 18 h, E/Z = 2:1, 90%; d) Grubbs cat. II (15 mol%), PhMe, 100°C, 18 h, E/Z = 2:1, 92%; e) 3 HF·Et_3N, THF/MeCN 1:1, 0°C to 23°C, **2**: 65%, **20**: 32%. CuTC = copper(I) thiophene-2-carboxylate, DMF = dimethylformamide.

dimerization of vinyl iodide **3** (ca. 10%). These unique yet effective conditions have been reported by Fürstner and co-workers and a series of sterically hindered substrates were successfully cross-coupled.[26] The resulting secondary alcohol **17** was then efficiently acylated with dienoic acid **5** under Yamaguchi esterification[27] conditions to give ester **18** in 86% yield. The subsequent RCM[28] of olefin **18** proceeded smoothly with the second generation Grubbs catalyst (15 mol%) to give a mixture of E/Z macrocycles in an overall yield of 90%. The initiation and conversion of this transformation were observed to be extremely fast and it could be conducted even at room temperature, intriguingly giving only the Z isomer **19** in this case. At 40°C, full conversion was observed within 10 min with E/Z ratio of 2:3, and further improvement to a ratio of 2:1 was possible through isomerization at elevated temperature. Interestingly, isomerization was not observed in the absence of the catalyst, thus suggesting that the thermodynamic equilibrium is most likely reached through ring-opening and ring-closing events. Fortunately, the two isomers were separable by column chromatography, which in turn allowed recycling of the Z isomer to give an 80% yield of E isomer **19** after one cycle. The final selective deprotection of the primary TBS ether and secondary TES ether was achieved in 65% yield by using triethylamine trihydrofluoride. In order to avoid unwanted over-deprotection, the reaction had to be stopped after a certain time to allow the isolation of TES-deprotected intermediate **20** (32%), which could be recycled to give more of the desired diol **2**. The aglycon **2** fulfills the criteria for a key building block for the completion of the total synthesis since it has the appropriate free hydroxy groups for the following glycosylations.

In summary, we report the preparation of the protected aglycon of fidaxomicin (**1**). The target macrocycle **2** was successfully synthesized in 14 steps (longest linear sequence) via three main fragments, thus allowing a considerable amount of flexibility in exploring the points of diversity for analogue synthesis. The highlights of our strategy include RCM between a terminal olefin and a dienoate moiety for macrocyclization, a diastereoselective VMAR, and a Stille coupling reaction of sterically hindered substrates. Currently, total synthesis of the natural product, including preparation of the noviose, rhamnose, and resorcinol units, as well as glycosylation studies, are in progress in our group.

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