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Synthesis of a Tiacumicin B Protected Aglycone

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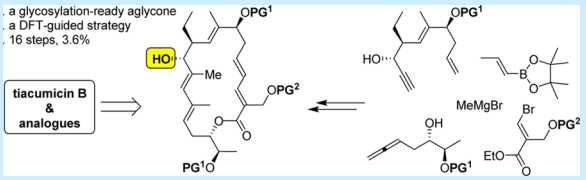
Supporting Information

ABSTRACT: Tiacumicin B is an antibiotic endowed with the remarkable ability to interact with a new biological target, giving it an inestimable potential in the context of the ever-growing and worrisome appearance of resistances of bacteria and mycobacteria to antibiotics. The synthesis of an aglycone of tiacumicin B ready for glycosylation is reported. The key steps of this approach are a [2,3]-Wittig rearrangement, a Pd/Cu-catalyzed allene−alkyne cross-coupling, a *E*-selective cross-metathesis, and a final ring-size selective macrolactonization.



Resistance to antibiotics is a serious re-emerging biomedical threat in rapid progression, with negative consequences on quality of life and significant economic impacts. It has become urgent to identify new molecules that interact with medicinally virgin biological targets so as to fight these resistances. Such molecules are scarce; however, tiacumicin B (**1**) (Figure 1), also

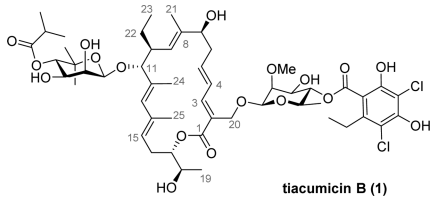
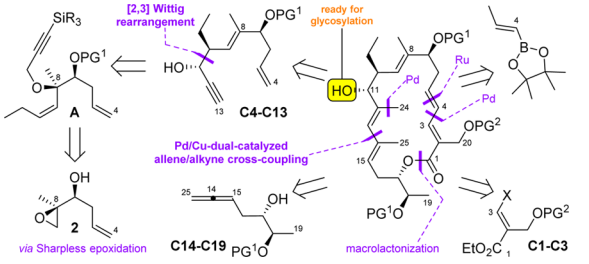


Figure 1. Tiacumicin B, a new antibiotic lead.

known as clostomicin B1, fidaxomicin, or lipiarmycin A_3,[1] belongs to this category. Tiacumicin B interacts with the β'-subunit of the switch region of the RNA polymerase (β'-*sr*-RNAP) and blocks it, which stops RNA synthesis and eventually leads to the death of bacteria.[2] The structure of the bacterial RNAP, and in particular the switch region, is conserved all across bacterial species but is different from the one of superior animals; therefore, a broad spectrum of bacteria could be covered selectively with only limited toxicity. This naturally occurring antibiotic, produced by fermentation, received FDA approval in 2011 in the USA for the treatment of a deadly nosocomial intestinal infection associated with *Clostridium difficile*.[3] β'-*sr*-RNAP is a drug target exploited since 2011, and no cross-resistance with any other antibacterial agents has yet appeared. Tuberculosis is another infection that can potentially be treated by blocking RNAP,[4] which is appreciable considering the emergence of multiresistant *Mycobacterium*.[5] Within this context, exploiting this new drug target is a unique opportunity that must be grasped by providing analogues of **1** with improved pharmacokinetic profiles or modified antibacterial spectra. Actually, chemical synthesis is likely the most efficient way to reach this goal. For all these reasons, but also because this complex polyketide/sugar mixed structure represents a beautiful synthetic challenge, tiacumicin B has already attracted the attention of the groups of Gademann[6] and Altmann,[7] who achieved the synthesis of its adequately protected macrolactonic core. The group of Zhu[8] synthesized the putative adequately protected macrolactonic core of lipiarmycin, a diastereomer of **1**. Ultimately, Gademann and co-workers recently achieved the total synthesis of tiacumicin B (**1**).[9]

The complexity of this structure authorizes numerous alternative approaches and is therefore a source of inspiration and strategic innovations. Scheme 1 depicts the strategy we designed for this synthesis. The [2,3]-Wittig rearrangement of propargyl allyl ethers is a powerful synthetic tool,[10] and we imagined it could allow building of the C_4−C_{13} fragment in a very straightforward and direct manner. Actually, through this single operation, a C−C bond would be created, and both the C_{10} and

Scheme 1. Retrosynthesis of the Tiacumicin B Aglycone



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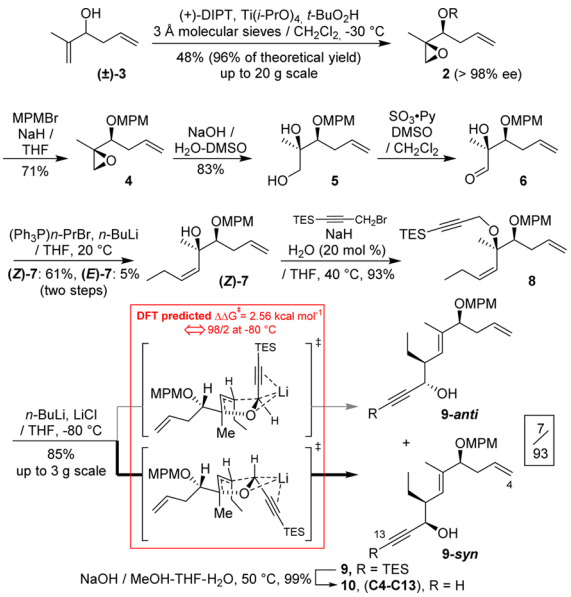
C_{11} stereogenic centers, as well as the configuration of the $C_8{=}C_9$ trisubstituted double bond, would be controlled simultaneously, thus offering an original access to the most densely functionalized fragment of our target. Unfortunately, the Wittig rearrangement of propargylic ethers of tertiary allylic alcohols such as **A** has been described only once and moreover with no diastereoselectivity.[11] So, albeit very attractive, this strategy appeared to be very risky, and this led us to carry out DFT calculations to evaluate its viability. Predictions showed that the transition state leading to the desired diastereomer laid 2.56 kcal mol^{-1} lower than the other possible one so a 99:1 *syn*/*anti* ratio was expected at −80 °C,[12] which prompted us to implement this Wittig rearrangement. This reaction providing the $C_4{-}C_{13}$ fragment as a terminal alkyne, we imagined using an allene/alkyne cross-coupling[13] for the assemblage with fragment $C_{14}{-}C_{19}$ that should therefore bear an allene function. The transformation of the resulting enyne into the desired diene seemed easily feasible considering the literature. To control the configuration of the alkene at C_4, we envisioned a cross-metathesis with a vinylboron derivative, a type of coupling partner known to give high *E* selectivity. This would be followed by a Suzuki−Miyaura cross-coupling to install fragment $C_1{-}C_3$. For the final step, we expected to perform a Yamaguchi macrolactonization with ring-size selectivity. Thus, the resulting aglycone having a nonprotected OH at position C_{11} would be glycosylation ready.

The construction of fragment $C_4{-}C_{13}$ commenced with the multigram scale synthesis of known allylic alcohol (±)-**3** (Scheme 2).[14] Kinetic resolution through Sharpless catalytic epoxidation[15]

Scheme 2. Synthesis of the $C_4{-}C_{13}$ Fragment



led to epoxy alcohol **2** (ee > 98%),[16] this step constituting therefore the sole source of chirality of the three stereogenic centers of the $C_4{-}C_{13}$ fragment. Epoxy alcohol **2** was protected as 4-methoxybenzyl ether **4** and hydrolyzed into diol **5** under basic conditions. A Parikh−Doering oxidation[17] led to sensitive hydroxy aldehyde **6**, which albeit non-OH-protected, underwent Wittig olefination successfully to furnish *Z* tertiary allylic alcohol **7** (*Z*/*E* 14:1, 61% yield of (**Z**)-**7** over two steps). We first met difficulties in obtaining propargylic ether **8**, but finally we found that the addition of 20 mol % of water to a suspension of NaH in THF allowed us to reach a yield of 93%. Then propargylic ether **8** was exposed to various strong bases to promote the key [2,3]-Wittig rearrangement (Table 1). Under conventional conditions:

Table 1. Improvement of the [2.3]-Wittig rearrangement of 8 into 9

entry	base (equiv)	solvent[a]−additive (equiv)	temp (°C)	yield[b] (%)	**9-*syn*/9-*anti*[c]**
1	*n*-BuLi (1.0)	THF	−80	38	76/24
2	*t*-BuLi (1.0)	THF	−80	55	71/29
3	LDA (1.2)	THF	−80	32	70/30
4	*n*-BuLi (1.0)	hexane	−80	trace	
5	*t*-BuONa (1.0)	THF	−80[d]	nr	
6	*n*-BuLi (1.0)	THF−HMPA (3.0)	−80	18	90/10
7	*n*-BuLi (3.0)	THF−LiCl (9.0)	−80[e]	**85**	**93/7**
8	*n*-BuLi (3.0)	THF−LiCl (9.0)	−100[f]	80	95/5
9	*n*-BuLi (3.0)	THF−LiCl (9.0)	+20	24	81/19
10	MeLi·LiBr (2.0)	THF−Et_2O	−80	74	85/15

[a]Concentration of **8** is 0.1 M. [b]Isolated yield. [c]Evaluated by ^1H NMR. [d]Room temperature reached before quench. [e]Quenched at −80 °C. [f]1 h of reaction before quench at −100 °C.

n-BuLi in THF at −80 °C and no additive (Table 1, entry 1), two diastereomers **9-*syn*** and **9-*anti*** were obtained in a 76/24 ratio in low yield. Nonetheless, in this first trial, the major product was of *syn* stereochemistry as DFT predicted, and this has encouraged us to optimize this transformation. There was no improvement when *t*-BuLi (entry 2) or LDA (entry 3) was used, and no reaction was observed with *n*-BuLi in hexane (entry 4). Interestingly, the use of HMPA as an additive (entry 6) led to an important improvement of the selectivity in favor of **9-*syn*** albeit in low yield. This result provided an interesting indication: the deaggregation of polymeric organolithium species has a positive impact on the selectivity. By forming homoaggregated organolithium species,[18] LiCl has similar properties, and actually its addition leads to spectacular yield and stereoselectivity improvements (85%, 93/7: *syn*/*anti*, entry 7) even reproducible on a 3 g scale. It has been reported that LiBr suppressed concurrent [1,2]-Wittig rearrangement,[19] but the effect of Li^+ on *syn*/*anti* selectivity has not been reported before. The use of MeLi·LiBr (entry 10) still led to a good yield, but with a lower selectivity. However, diastereomers **9-*syn*** and **9-*anti*** remained inseparable even by preparative HPLC.[20] Finally, the TES protective group of **9** was easily removed using aqueous NaOH affording key intermediate **10** obtained from **3** in eight scalable steps with an overall yield of 27%. ^1H and ^{13}C NMR chemical shifts of all possible stereoisomers of **9** were simulated by DFT, indicating that its structure is very likely the one expected.[12] To provide a univocal structural confirmation, alcohol **10** was protected as silyl ether **11** and the alkyne function of **11** was transformed into the corresponding vinylboronic ester **12** through methyl boration[21] and then into vinylic iodide[22] **13** (Scheme 3). Removing the MPM protective group[23] gave **14**[7] that has been used by Altmann for his own synthesis of the tiacumicin B aglycone.

We accessed allene **18-*anti*** ($C_{14}{-}C_{19}$ fragment) from (*R*)-2-methyloxirane (Scheme 4).[24] Opening of the latter by nucleophilic attack of sodium thiophenolate and one-pot protection as a 4-methoxybenzyl ether led to **15**. The thioether was oxidized into sulfoxide **16**, and a Pummerer rearrangement[25]/acidic hydrolysis/Luche propargylation[26] sequence led to homopropargylic alcohol **17** as a ca. 1/1 *syn*/*anti* mixture in 81%. These two diastereoisomers were difficult to separate so they

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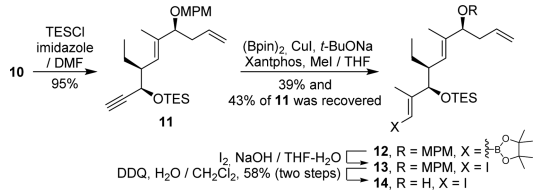
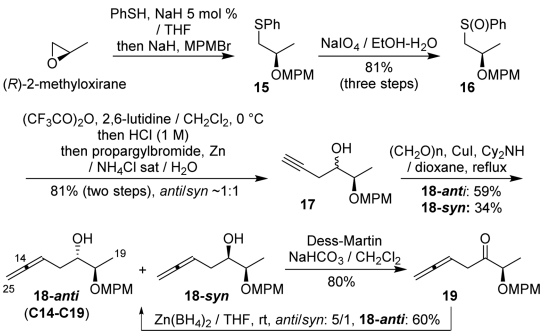
Scheme 3. Structure Confirmation of the Fragment 10



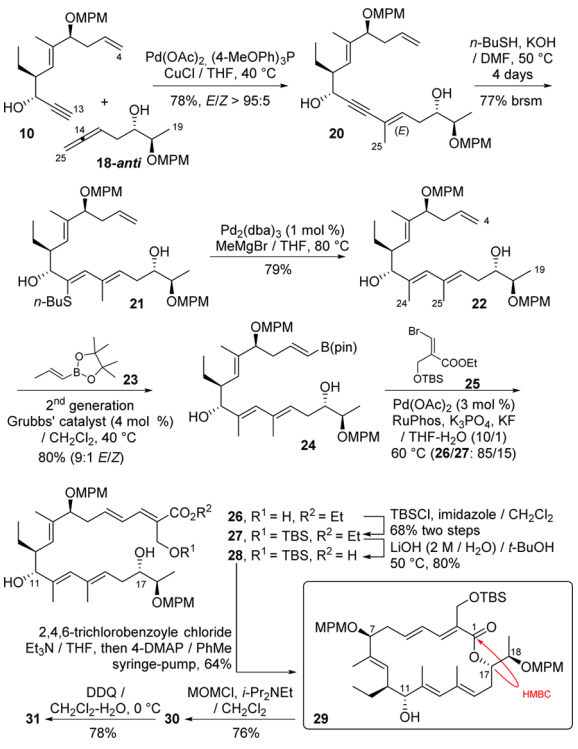
Scheme 4. Synthesis of the C_{14}–C_{19} Fragment 18-*anti*



were both transformed[27] into HPLC-separable allenes **18-*syn*** and **18-*anti***. Allene **18-*syn*** can be recycled and converted into **18-*anti*** *via* ketone **19** and selectively reduced.[28]

The assemblage of fragments C_4–C_{13} (**10**) and C_{14}–C_{19} (**18-*anti***) was then addressed. We used the planned alkyne/allene cross-coupling[13] which led to enyne **20** in good yield (78%, E/Z > 95:5, Scheme 5). To the best of our knowledge, this is the first implementation of this reaction in total synthesis. We had now to transform this enyne function into the desired diene and also install the missing C_{24}-methyl group. The simplest way to do this

Scheme 5. Assemblage of Fragments C_4–C_{13} with C_{14}–C_{19} and Final Cyclization Steps



consisted in using the Duboudin reaction on **20**.[29] However, this approach failed. The Fürtsner's ruthenium-catalyzed OH-directed hydrosilylation[30] installed the silicium at the wrong distal position in low yield, and radical OH-directed hydrostannylation with Ph_3SnH[31] led to degradation. Finally, regio- and *trans*-selective nucleophilic alkyne hydrosulfuration[32] of enyne **20** yielded vinyl sulfide **21** efficiently. Ni-catalyzed cross-coupling completely failed to install the missing methyl C_{24} from vinyl sulfide **21**. An unusual ligand-free Pd-catalyzed Kumada–Corriu cross-coupling[33] finally enabled us to introduce efficiently the methyl-24 on the C_4–C_{19} fragment to give key compound **22**. It is noteworthy that no protective group was necessary to perform the whole coupling/hydrosulfuration/methylation sequence. In addition, this strategy constitutes an innovative alternative to those traditionally based on the protocols of Suzuki, Negishi, and Stille, with the advantage of requiring no preactivation of both cross-coupling partners under the form of a [halide/organometallic] couple, which is a gain in terms of time, number of steps, and amount of waste produced. Ultimately, we broached the final stages of this synthesis. For this we could have follow one of the previously described pathways based on ring-closure or cross-metathesis strategies.[6−9] However, the various *E* selectivities at position 4 reported there, were unsatisfactory unless an additional isomerization step was used. As planned, we used vinylboronate **23** as cross-metathesis partner,[34,35] and **22** was transformed into boronic ester **24**, with as expected a 9/1 E/Z ratio, using only 4 mol % of Grubbs' second-generation catalyst, and with an 80% yield (Scheme 5).

A Suzuki–Miyaura cross-coupling with brominated compound **25**[36] using the RuPhos ligand[37] led to diene **27** in a good yield albeit with the loss of the TBS protective group (compound **26**). The latter was selectively reinstalled to give **27** in a high yield. A saponification gave seco-acid **28**. Cases of ring-size-selective macrolactonizations with the Yamaguchi[38] reaction have been reported,[39] and in our case it seemed likely that the desired 18-membered lactone would prevail over the 12-membered one.[40] DFT calculations showed us that the 18-membered ring laid 25.1 kcal mol^{-1} lower than its concurrent 12-membered ring,[12] and gratifyingly, ring-size selectivity occurred[12] as diol **28** cyclized into macrolactone **29** in a 64% yield. Advantageously, with its OH function at C11 remaining nonprotected, aglycone **29** is ready for the next glycosylation step with D-noviose. We are currently optimizing a substrate-directed 1,2-*cis* selective[41] noviosylation to complete our total synthesis of tiacumicin B. The relevance of the use of MPM groups to protect the OH at C_7 and C_{18} was confirmed. Their removal step has been planned for the very end of the total synthesis of tiacumicin B (**1**) where, in particular, the oxidizable OH at C_{11} is engaged in a glycosidic bond with D-noviose. Therefore, this step was tested on compound **30** which bears a MOM group on this OH, thus mimicking a glycosidic linkage. We were pleased to see that under classical oxidative conditions[23] the two MPM groups were cleanly removed to furnish diol **31** with a 78% yield, thus indicating that our protective groups choice will very likely allow the achievement of the total synthesis of tiacumicin B.

In conclusion, we have achieved the synthesis of an adequately protected tiacumicin B aglycone. Starting from known alcohol (±)-**3**, this synthesis was performed with a 3.6% overall yield in 16 steps (longest linear sequence), of which only four dealt with installation or removal of protective groups. DFT predictions prompted us to use a strategically risky [2,3]-Wittig rearrangement of the propargyl ether of a tertiary allylic alcohol, allowing us to synthesize the most densely functionalized fragment of the

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target in a very direct way and with high selectivity. We also built the tetrasubstituted $C_{12}-C_{15}$ diene stereoselectively using an innovative strategy based on the sequence allene−alkyne Pd/Cu-dual catalyzed cross-coupling/selective hydrosulfuration/Pd-catalyzed Kumada−Corriu cross-coupling of an alkenylsulfide function. To finish this synthesis, a cross-metathesis using a vinylboronate allowed high control of the *E* configuration of the $C_4{=}{=}C_5$ bond, and a Suzuki−Miyaura cross-coupling was used to install the missing C_1-C_3 fragment. As anticipated, the final macrolactonization step revealed itself to be ring-size-selective, delivering a glycosylation-ready aglycone of tiacumicin B.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01744.

Experimental procedures, characterization data, and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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