Total Synthesis of Tiacumicin B: Implementing H-bond-Directed Acceptor Delivery for Highly Selective β-Glycosylations

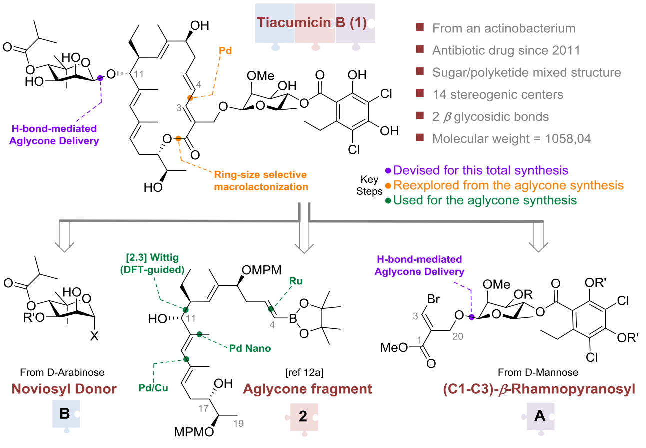
Stéphanie Norsikian,*[a] Cedric Tresse,[a] Marc François-Eude,[a] Louis Jeanne-Julien,[b] Guillaume Masson,[b] Vincent Servajean,[a] Grégory Genta-Jouve,[b] Jean-Marie Beau,[a,c] and Emmanuel Roulland*[b]

[a] Dr. C. Tresse, Dr. M. François-Eude, V. Servajean, Prof. J.-M. Beau, Dr. S. Norsikian, Institut de Chimie des Substances Naturelles ICSN-CNRS, Centre de Recherche de Gif,Avenue de la Terrasse, 91198, Gif-sur-Yvette (France).
[b] Dr. L. Jeanne-Julien, Dr. G. Masson, Dr. G. Genta-Jouve, Dr. E. Roulland, C-TAC, CitCom, UMR 8038, CNRS-Université de Paris, Faculté de Pharmacie, 4, avenue de l'Observatoire, 75006, Paris (France).
[c] Prof. J.-M. Beau, Laboratoire de Synthèse de Biomolécules, ICMMO, UMR 8182, Univ. Paris-Sud and CNRS, Université Paris-Saclay, F-91405 Orsay, France
E-mail : emmanuel.roulland@parisdescartes.fr

Abstract: *We report a total synthesis of tiacumicin B, one of the most structurally complex natural antibiotic macrolides. Endowed with remarkable biological properties, it is used to treat very severe intestinal infections. The strategy is in part based on our experience of the synthesis of the tiacumicin B aglycone, and on the decisive implementation of an H-bond-mediated Aglycone Delivery (HAD) using sulfoxides as anomeric leaving-groups. This new HAD variant permitted highly β-selective rhamnosylation and noviosylation. To increase the convergence, the rhamnosylated C1-C3 fragment thus obtained was anchored to the C4-C19 aglycone fragment by adapting the reliable Suzuki-Miyaura cross-coupling conditions used for the aglycone synthesis. The ring-size selective macrolactonization provided a compound engaged directly in the noviolysation step with a virtually total β-selectivity. The final and efficient removal of all the protective groups (PGs) provided synthetic tiacumicin B.*

Tiacumicin B (Tcn-B, **1**) –also known as clostomicin B1, fidaxomicin or lipiarmycin A3– (Scheme 1), was isolated for the first time in 1975 from *Dactylosporangium aurantiacum*, an actinobacterium.[1] Consisting of an 18-membered macrolactonic core decorated by two rare sugars (D-noviose and D-rhamnose) attached through β glycosidic bonds, displaying 14 stereogenic centers and several polysubstituted alkenes, Tcn-B is one of the most complex antibiotic-macrolides. This structural complexity induces a high degree of synthetic difficulty, whose the thorny problem of the 1,2-cis glycosylations.[2] The occurrence of drug-resistant superbugs is no longer just a frightening prediction for the future. This serious biomedical risk is already a major threat to public health, degrading the quality of life, and severely impacting the economy. Hence, finding new antibiotics with new biological targets is essential to circumvent resistances. Tcn-B is one of these and received a fast-track FDA approval in 2011 for the treatment of serious gut infections associated with *Clostridium difficile*, and frequently nosocomial and fatal.[3] Tcn-B eradicates bacteria by inhibiting the RNA polymerase, targeting the "switch-region".[4] Cross-resistance with other antibiotics is very unlikely,[5] even with rifamycin because, although close, the targeted domains do not overlap, so that rifamycin-resistant forms of *Mycobacterium tuberculosis* remain highly sensitive to Tcn-B.[6] There is therefore a strong demand for analogues of Tcn-B, and hence for a reliable total synthesis of it. In addition to its antibiotic properties, the daunting structure of Tcn-B is very inspiring in the eyes of synthesis chemists, explaining why several renowned research groups have embarked in the adventure of its total synthesis.[7] In 2015 Gademann[8] and Altmann,[9] published the first syntheses of the aglycone of Tcn-B, Zhu[10] reporting the synthesis of a diastereomer.

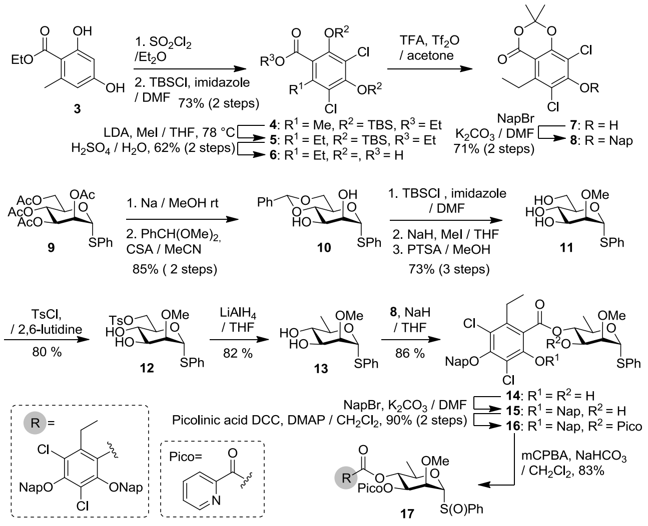
Total synthesis of complex natural products is a naturally conducive ground for discovery and innovations.[11] The conception of our two synthetic pathways towards the aglycone,[12] and in particular the original strategy we designed to synthesize the C12-C15 diene, resulted in the discovery that Pd-nanoparticles catalyze the Kumada-Corriu reaction of vinylsulfides,[13] and to propose an unprecedented mechanism for the Grigg allene/alkyne cross-coupling.[14] Despite the considerable amount of energy deployed, only Gademann had so far been capable of completing the total synthesis of Tcn-B, providing solutions to the thorny β-glycosylations problem:[15,16] *a)* The Helferich's protocol (activating agent: $HgO_{(excess)}/HgBr_{2(cat)}$)[17] was used for the noviosylation of an aglycone fragment (α/β: 1/3, β : 54%), the cyclic aglycone always leading to α adducts whatever conditions used. *b)* The rhamnosylation was carried out on the macrolide, using an imidate donor (α/β: 1/4, β : 62%). Following this strategy, Gademann also synthesized three congeners of Tcn-B: tiacumicin A,[16] and mangrolide A[18] and D.[19] In 2019, de Brabander also reported a total synthesis of mangrolide D.[20]



Scheme 1. Tiacumicin B (**1**) and our retrosynthetic analysis

The new total synthesis of tiacumicin B (**1**) we depict here is based on strategic and methodological innovations that allow an original and selective assemblage of the three main regions of the molecule (Scheme 1). It naturally relies on our synthesis of the Tcn-B aglycone, whose strategy had been designed with an eye to the total synthesis. Originally, we had imagined glycosylating our aglycone sequentially, a probably viable pathway. However we finally opted for a less traditional but more convergent retrosynthetic plan. In this scenario, Tcn-B was disconnected into fragments **A**, **B**, and the known **2**,[12a] equivalent in size and complexity. We chose to assemble fragment **A** together with fragment **2** first, then close the macrolactone, and install fragment **B** at the very end. The Suzuki coupling developed during our aglycone synthesis[12a] was considered robust enough to allow assembling fragments **2** with fragment **A**, instead of the small silylated C1-C3 fragment formerly involved, thus adding convergence. This approach reduces risks of failure since rhamnosylation conditions needed for the synthesis of **A** can be developed using the C1-C3 fragment as acceptor, which is structurally simple and easily accessible. A complete ring-size selectivity had been observed previously during the aglycone macrolactonization. Applied to this total synthesis, this step should provide a monoglycosylated macrolactone bearing at C11 an unprotected OH directly ready for the *β*-noviosylation step. This exciting scenario was nonetheless uncertain for at least three reasons: *a)* noviosylation is a very late step, *b)* a high *β*-selectivity is required, and *c)* this macrolactone has been described as a reluctant glycosylation acceptor.[16]

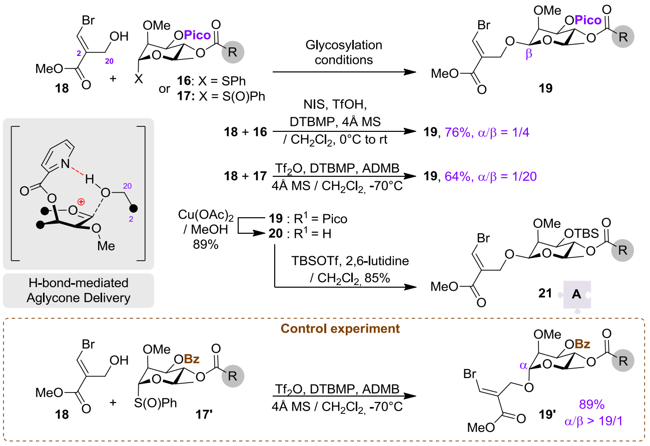
To prepare fragment **A** we considered using a *β*-selective glycosylation of acceptor **18** (Scheme 3) by the phenylthio-rhamnosyl donor **16** that bears a picoloyl group (Pico) at *O*-3 (Scheme 2).



Scheme 2. Rhamnopyranosyl donors **16** and **17** syntheses. TFA: trifluoroacetic acid, NapBr: 2-naphthalene-methyl-bromide, LDA: lithium di-*iso*-propylamide, CSA: camphorsulfonic acid, PTSA: paratoluene sulfonic acid, DCC: dicyclohexylcarbodiimide, DMAP: 4-dimethylaminopyridine, *m*-CPBA: 3-chloroperoxybenzoic acid.

As described by Demchenko,[21] a remotely positioned Pico group can direct, through intermolecular H-bonding, a selective facial attack on the glycosyl donor. We started with the synthesis of the homodichloro orsellinate attached to the rhamnoside. Commercially available orcellinate **3** was dichlorinated, and both phenols protected by *tert*-butyldimethylsilyl groups providing **4**. The benzylic methyl group was deprotonated with LDA then methylated giving **5**. Acidic hydrolysis led to deprotected carboxylic acid **6** that upon a treatment with acetone and Tf_2O in trifluoroacetic acid furnished cyclic ester **7**. The remaining free phenol of **7** was protected, supplying 2-naphthalene-methyl (Nap) ether **8**.

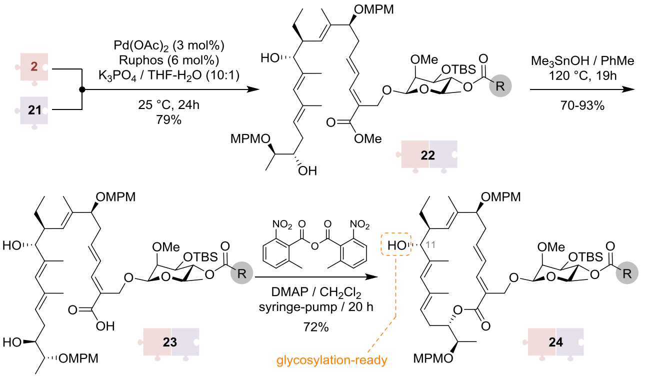
We then addressed the rhamnosyl donor synthesis starting from phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-manopyranoside **9** (Scheme 2). Diol **10** was obtained through a Zemplén deacetylation and a 4,6-benzylidene formation. Then **10** was selectively TBS-protected at *O*-3, methylated at *O*-2, and deprotected (PTSA/methanol) furnishing triol **11**. Selective tosylation in 2,6-lutidine gave **12**, whose reduction with LAH provided the desired rhamnose derivative **13**. Gademann's conditions allowed assembling ester **8** together with diol **13** giving selectively **14**.[15] The free phenol of **14** was protected as a Nap ether **15**, and the rhamnoside *O*-3 position was esterified with picolinic acid. This led to the expected donor **16** ready for glycosylation of alcohol **18**[22] (Scheme 3).



Scheme 3. Glycosylation conditions and synthesis of fragment **A**. NIS: *N*-iodosuccinimide, DTBMP: 2,6-di-terbutyl-4-methylpiridine, ADMB: 4-allyl-1,2-dimethoxybenzene.

Initial glycosylation attempts carried out in 1,2-dichloroethane with dimethyl(methylthio)sulfonium triflate, a classical promoter of H-bond-mediated Aglycone Delivery (HAD),[21] were disappointingly unsuccessful. First promising coupling results of donor **16** with acceptor **18** were obtained using *N*-iodosuccinimide (1 equiv/donor) and triflic acid (0.92 equiv/donor)[23] in CH_2Cl_2 at –40 °C to rt and produced **19** (76%, α/β: 1/4),[24] whose anomers was separated by prep-HPLC. Seeking much higher *β*-selectivity, we shifted to sulfoxide **17** featuring an anomeric leaving-group never used before in HAD. In this case, donor **17** (1.7 eq.) was activated using Tf_2O in CH_2Cl_2 at –70 °C in the presence of the acceptor **18**, DTBMP, and ADMB.[25, 26] We were pleased to find that the desired glycosylated compound **19** was formed with a high facial selectivity (α/β : 1/20), with 64% yield. To verify that this glycosylation well took place through HAD, we made a control experiment using donor **17'**, an analog of **17** whose picoloyl was replaced by a benzoyl. Product **19'** was the only one to form here, its α configuration indicating that the picoloyl group on donor **17** could direct remotely the nucleophilic attack to the *β*-face likely thanks to the formation of a H-bond. The picoloyl of **19** was then easily removed with $Cu(OAc)_2$, and replaced by a TBS to lead to fragment **A** (**21**).

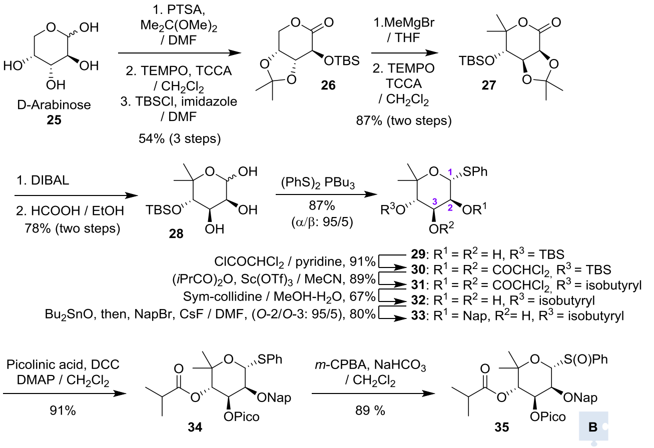
Our synthesis of aglycone fragment **2** was robust enough to be scaled up.[12a] We were pleased to see that after modifying slightly the conditions formerly used, the convergent step of Pd-catalyzed cross-coupling of **2** with rhamnoside **21** proceeded cleanly, providing ester **22** with 79% yield (Scheme 4).



Scheme 4. Assemblage of **2** and **A**, and macrolactonization. MPM: 4-Methoxyphenylmethyl, Ruphos: CAS number: 787618-22-8.

A critically important selectivity was needed to convert **22** into seco-acid **23** since a second ester function was present on the rhamnoside moiety. This was achieved by using Me$_3$SnOH in toluene at 120 °C giving **23** with yields of 70 to 93%.[27] With seco-acid **23** in hand, we focused on the macrolactonization expecting again ring-size selectivity. However, the strict transposition of the Yamaguchi conditions[28] we had used before, led to the desired hemi-glycosylated tiacumicin B **24** with only 23% yield. The Boden-Keck's protocol,[29] allowed reaching 58% yield, but **24** proved a mixture of two products resulting from the isomerization of the C4-C5 alkene. Finally, the Shiina's conditions[30] allowed a far cleaner and reproducible macrolactonization into **24** with 72% yield, and an isomerization minimized at 15%. Our strategy allowed OH at C11 to remain protective-group-free throughout this synthesis, so that **24** could be directly engaged in the noviosylation step.

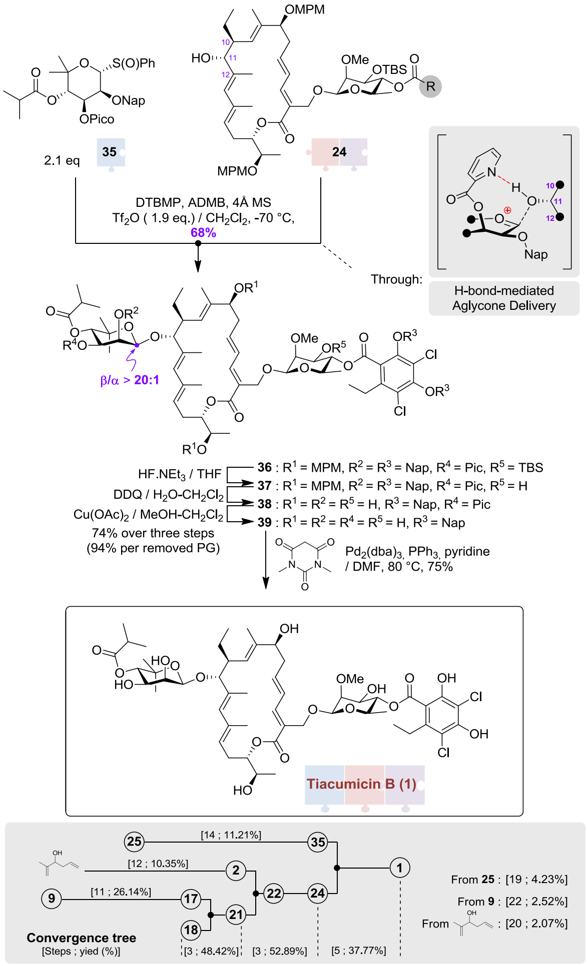
At first, to secure good *β*-selectivity, we had programmed anchoring the noviose using a silicon tether delivery.[31] This strategy failed in our case, so we decided implementing again an HAD approach with a directing picoloyl group at *O*-3 of the sugar. Thus, the required noviosyl donor was prepared from D-arabinose **25** (Scheme 5). The latter was transformed into lactone **26** through selective acetonide protection, oxidation of the lactal, and silylation of the remaining OH group. Lactone **26** was treated with MeMgBr then oxidized into lactone **27**. Dibal-H reduction of **27** led to the corresponding lactol whose acetonide protection was removed under mild acidic conditions leading to **28**. A thiophenyl group was then installed at the anomeric position giving diol **29**, which was protected as bis-dichloroacetyl ester **30**. Treatment by (*i*PrCO)$_2$O and a catalytic amount of Sc(OTf)$_3$ in MeCN allowed the direct replacement of the TBS group by an isobutyrate leading to **31**.[32] The two dichloroacetates of **31** were then selectively removed with *sym*-collidine giving diol **32**. Through the intermediate stannylene of **32**, and a NapBr/CsF treatment, a Nap PG was introduced at the *O*-2 position leading to alcohol **33** with an unexpectedly high selectivity.[33] Alcohol **33** was esterified with picolinic acid using DCC to give sulfide **34**, the desired noviosyl donor. Preliminary trials using (+)-menthol as acceptor led predominantly to the *β*-adduct (*α*/*β*: 1/5) in 72 % yield demonstrating the feasibility of this approach. Unfortunately, the reactions with macrolactonic acceptor **24** was unsuccessful, no glycosylated adduct being detected.[16]



Scheme 5. Noviosyl donor synthesis. TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy, TCCA: trichloroisocyanuric acid.

The success of the above-mentioned rhamnosylation led us to consider that sulfoxide **35** could be a superiorly reactive donor. Under our activation conditions (Tf$_2$O activation of **35** in the presence of **24**, DTBMP, ADMB/CH$_2$Cl$_2$, –70 °C) we were pleased to isolate the desired noviosylated product **33** with 68% yield, with a virtually total facial selectivity ($\alpha/\beta > 1/20$).[34]

The very last steps of this total synthesis consisted in removing seven PGs from compound **36**: 2 MPMs, 3 Naps, 1 Pico and 1 TBS. First, the TBS group located on the rhamnoside moiety was cleaved using HF.NEt$_3$ giving alcohol **37** (Scheme 5). The 2 MPMs, as well as the Nap located at *O*-2 on the novioside, were readily oxidized by DDQ at 0 °C leading to **38** in 3 hours. However, the two Naps on the phenol functions of the rhamnoside proved resistant to these smooth conditions, and an extended reaction time at r.t. produced an intractable mixture of products. Nonetheless, the removal of the Pico was cleanly carried out (Cu(OAc)$_2$/methanol-CH$_2$Cl$_2$, 0 °C) giving **39**. Importantly, the Pico group had to be removed after the Nap otherwise DDQ would lead to the formation of a 2-naphthylmethylidene bridge over *O*-2 and *O*-3 of the novioside. These three operations proved very clean and were performed without intermediate purification giving **39** with an overall 74% yield (94% per PG). Finally, we had to address what turned out to be a tricky final problem: the cleavage of the two reluctant Nap groups protecting the phenol functions. Mild Pd-catalyzed hydrogenation conditions failed at being selective.[35] However, we had previously observed that Suzuki cross-coupling conditions used to create the C3-C4 bond of the aglycone led, when conducted at 80 °C, to a partial loss of the Nap groups of these phenols. Exploiting this, we developed Pd-catalyzed conditions (Pd$_2$(dba)$_3$/4.PPh$_3$, 1,3-dimethylbarbituric acid, pyridine/DMF, 80 °C) that ultimately provided tiacumicin B (**1**) cleanly and with a good yield. This 4-steps removal of the 7 PGs took place with 55.5% overall yield (91.9% per PG). The physicochemical data of our synthetic Tcn-B are strictly identical to those of the naturally occurring compound; $\alpha^{23}_D = -5.6$ deg cm^3 g^{-1}dm^{-1} (c= 0.41 g/100 cm^3, MeOH), lit.:[1b] ($\alpha^{23}_D = -5.5$ deg cm^3 g^{-1}dm^{-1} (c=1.98 g/100 cm^3, MeOH).



Scheme 6. Noviosylation and PGs removal. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In summary, we have achieved the total synthesis of tiacumicin B (**1**), with as salient steps the highly *β*-selective rhamnosylation, the Suzuki cross-coupling that allowed assembling the rhamnoside **21** with aglycone fragment **2**, the ring-size selective macrolactonization, the final and virtually totally selective *β*-noviosylation of the cyclic aglycone, and the successful removal of all PGs. The remarkable facial selectivity of both glycosylations relies on an H–bond-directed effect of a remote 3-*O*-picoloyl group set on the incoming glycosyl acceptors, and the conjoint use of a phenylsulfoxide leaving-group. We believe that this new variant of the Demchenko procedure will prove useful to address the biological relevance of the carbohydrate moieties of tiacumicin B or other sensitive aglycones through the preparation of a set of glycosylated analogues.

Acknowledgements

We gratefully acknowledge financial supports from the French Agence Nationale pour la Recherche (ANR-14-CE16-0019-02, SYNTIA project), the CNRS, and the Université de Paris. We thank V. Steinmetz for HPLC support.

Keywords: antibiotics • natural products • total synthesis • catalysis • enantioselective synthesis • glycosylation

---

(1) Firstly isolated: a) F. Parenti, H. Pagani, G. Beretta, *J. Antibiot.* **1975**, *28*, 247-252. b) C. Coronelli, R. J. White, G. C. Lancini, F. Parenti, *J. Antibiot.* **1975**, *28*, 253-259. c) Amura S., Imamura N., Oiwa R., Kuga H., Iwata R., Masuma R., *J. Antibiot.* **1986**, *39*, 1407–1412.d) Theriault R. J., Karwowski J. P., Jackson M., Girolami R. L., Sunga G. N., Vojtko C. M., *J. Antibiot*. **1987**, *40*, 567–574. e) Hochlowski J. E., Swanson S. J., Ranfranz L. M., Whittern D. N., Buko A. M., McAlpine J. B., *J. Antibiot*. **1987**, *40*, 575–588. f) A. Bedeschi, P. Fonte, G. Fronza, C. Fuganti, S. Serra, *Nat. Prod. Commun.* **2014**, *9*, 237-240; Some ambiguity existed concerning the structure of tiacumicin B and its relatives, for clarifications see: g) W. Erb, J. Zhu, *Nat. Prod. Rep.* **2013**, *30*, 161–174.

(2) For a recent review see: S. S. Nigudkar and A. V. Demchenko, *Chem. Sci.* **2015**, *6*, 2687-2704.

(3) Traynor K., *Am. J. Health Syst. Pharm*. **2011**, *68*, 1276.

(4) a) A. Tupin, M. Gualtieri, J.-P. Leonetti, K. Brodolin, *EMBO J.* **2010**, *29*, 2527-2537. b) M. Gualtieri, A. Tupin, K. Brodolin, J.-P. Leonetti, *Int. J. Antimicrobial Agents* **2009**, *34*, 605-616.

(5) A. Srivastava, M. Talaue, S. Liu, D. Degen, R. Y. Ebright, E. Sineva, A. Chakraborty, S. Y. Druzhinin, S. Chatterjee, J. Mukhopadhyay, Y. W. Ebright, A. Zozula, J. Shen, S. Sengupta, R. R. Niedfeldt, C. Xin, T. Kaneko, H. Irschik, R. Jansen, S. Donadio, N. Connell, R. H Ebright *Current Opinion in Microbiology* **2011**, *14*, 532-543.

(6) M. Kurabachew, S. H. Lu, P. Krastel, E. K. Schmitt, B. L. Suresh, A. Goh, J. E. Knox, N. L. Ma, J. Jiricek, D. Beer, M. Cynamon, F. Petersen, V. Dartois, T. Keller, T. Dick, V. K. *J.* Sambandamurthy, *Antimicrob. Chemother* **2008**, *62*, 713-719.

(7) For a review on the various synthetic approaches see: E. Roulland *Synthesis* **2018**, *50*, 4189-4200.

(8) H. Miyatake-Ondozabal, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed.* **2015**, *54*, 1933-1936. *Angew. Chem*. **2015**, *127*, 1953-1956.

(9) F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed*. **2015**, *54*, 1937-1940. *Angew. Chem*. **2015**, *127*, 1957-1961.

(10) W. Erb, J.-M. Grassot, D. Linder, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed*. **2015**, *54*, 1929-1932. *Angew. Chem*. **2015**, *127*, 1949-1952.

(11) P. S. Baran *J. Am. Chem. Soc*. **2018**, *140*, 4751−4755.

(12) a) L. Jeanne-Julien, G. Masson, E. Astier, G. Genta-Jouve, V. Servajean, J.-M. Beau, S. Norsikian, E. Roulland *Org. Lett.* **2017**, *19*, 4006 – 4009. b) L. Jeanne-Julien, G. Masson, E. Astier, G. Genta-Jouve, V. Servajean, J.-M. Beau, S. Norsikian, E. Roulland *J. Org. Chem.* **2018**, *83*, 921 – 929.

(13) L. Jeanne-Julien, E. Astier, R. Lai-Kuen, G. Genta-Jouve, E. Roulland *Org. Lett*. **2018**, *20*, 1430-1434.

(14) L. Jeanne-Julien, G. Masson, R. Kouoi, A. Regazzetti, G. Genta-Jouve, V. Gandon, E. Roulland *Org. Lett.* **2019**, 21, 3136-3141.

(15) E. Kaufmann, H. Hattori, H. Miyatake-Ondozabal, K. Gademann *Org. Lett.* **2015**, *17*, 3514-3517.

(16) H. Hattori, E. Kaufmann, H. Miyatake-Ondozabal, R. Berg, K. Gademann, *J. Org. Chem.* **2018**, *83*, 7180-7205.

(17) B. Helferich, K. F. Wedemeyer, *Liebigs Ann. Chem.* **1949,** *563*, 139-145.

(18) H. Hattori, J. Roesslein, P. Caspers, K. Zerbe, H. Miyatake-Ondozabal, D. Ritz, G. Rueedi, K. Gademann, *Angew. Chem. Int. Ed.* **2018**, *57*, 11020-11024. *Angew. Chem*. **2018**, *130*, 11186-11190.

(19) H. Hattori, L. V. Hoff, K. Gademann *Org. Lett.* **2019**, *21*, 3465-3459.

(20) J. Gong, W. Li, P. Fu, J. MacMillan, J. K. De Brabander *Org. Lett.* **2019**, *21*, 2957-2961.

(21) a) J. P. Yasomanee and A. V. Demchenko, *J. Am. Chem. Soc.* **2012**, *134*, 20097-20102. b) S. G. Pistorio, J. P. Yasomanee, A. V. Demchenko, *Org. Lett*. **2014**, *16*, 716–719.

(22) See the SI for the preparation

(23) The reaction was unsuccessful with a catalytic amount of TfOH

(24) Stereochemistry determined by measuring $^1J_{C1,H1}$ coupling: ≈160 Hz indicates that H-1 is axial, and ≈170 Hz equatorial.

(25) J. Gildersleeve, A. Smith, K. Sakurai, S. Raghavan, D. Kahne, *J. Am. Chem. Soc.* **1999**, *121*, 6176-6182.

(26) J. Zeng, Y. Liu, W. Chen, X. Zhao, L. Meng, Q. Wan, *Top Curr Chem* **2018**, *376*, 27-59.

(27) K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina*, Angew. Chem. Int. Ed*. **2005**, *44*, 1378-1382. Angew. Chem. 2005, 117, 1402-1406.

(28) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

(29) a) E. P. Boden, G. E. Keck, *J. Org. Chem.* **1985**, *50*, 2394-2395. b) G. E. Keck, E. P. Boden, M. R. Wiley, *J. Org. Chem*. **1989**, *54*, 896-906.

(30) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822-1830.

(31) a) G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087. b) M. Bols, *J. Chem. Soc., Chem. Commun.* **1992**, 913-914. c) J. T. Walk, Z. A. Buchan, J. Montgomery, *Chem. Sci.* **2015**, *6*, 3448-3453.

(32) S. Norsikian, I. Holmes, F. Lagasse, H. B. Kagan, *Tetrahedron Lett.* **2002**, *43*, 5715-5717.

(33) A $^3J_{1,2}$ coupling constant of 9.5 Hz in the ^{1}H NMR spectrum of diol **32** indicates a H-1/H-2a *trans* diaxial orientation. Therefore, the conformation of the starting diol is not a conventional $^4C_1$ chair but rather a $^1C_4$ chair certainly imposed by the presence of the gem-dimethyl group. The equatorial OH is more accessible, which accounts for the selectivity of this protection.

(34) The α anomer could not be detected in ^{1}H NMR spectrum.

(35) A B. Smith, III, C. Sfouggatakis, C. A. Risatti, J. B. Sperry, W. Zhu, V. A. Doughty, T. Tomioka, D. B. Gotchev, C. S. Bennett, S. Sakamoto, O. Atasoylu, S. Shirakami, D. Bauer, M. Takeuchi, J. Koyanagi, Y. Sakamoto, *Tetrahedron*, **2009**, *65*, 6489-6509.