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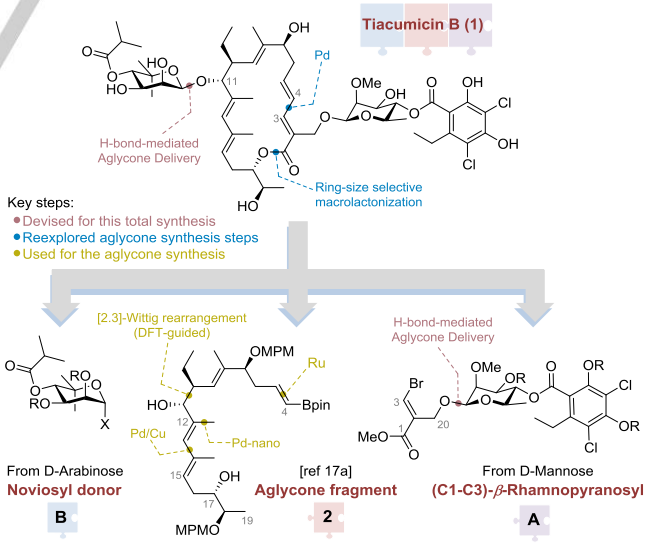
Total Synthesis of Tiacumicin B: Implementing H-bond-Directed Acceptor Delivery for Highly Selective β-Glycosylations

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]

Dedicated to Professor Henri-Philippe Husson

Abstract: *We report a total synthesis of tiacumicin B, a natural macrolide whose remarkable antibiotic properties are used to treat severe intestinal infections. The strategy is in part based on our experience of the synthesis of the tiacumicin B aglycone, and on the decisive use of sulfoxides as anomeric leaving-groups in H-bond-mediated Aglycone Delivery (HAD). This new HAD variant permitted highly β-selective rhamnosylation and noviosylation. To increase convergence, the rhamnosylated C1-C3 fragment thus obtained was anchored to the C4-C19 aglycone fragment by adapting the reliable Suzuki-Miyaura cross-coupling used for the aglycone synthesis. Ring-size selective macrolactonization provided a compound engaged directly in the noviolysation step with a virtually total β-selectivity. The final 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), is a molecule 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 therefore one of the most complex antibiotic-macrolides known. A high degree of synthetic difficulty arises from such a structural complexity, whose the thorny problem of the 1,2-cis glycosylations.[2] Resistance to antibiotics has become a serious biomedical risk and a major threat to public health with sever impacts on the economy. In this context the finding of new antibiotics with new biological targets is essential. Tcn-B being one of them it received a fast-track FDA approval in 2011 for the treatment of frequently nosocomial and fatal gut infections associated with *Clostridium difficile*.[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 domains targeted do not overlap so that rifamycin-resistant forms of *Mycobacterium tuberculosis* remain highly sensitive to Tcn-B.[6] The demand for Tcn-B analogues is therefore strong and calls for the setting of reliable total synthesis pathways. The daunting structure of Tcn-B has inspired several renowned research groups to embark in the adventure of its total synthesis.[7] In 2015 Gademann[8] and Altmann,[9] published the two firsts syntheses of the aglycone of Tcn-B, and Zhu[10] the synthesis of a diastereomer. Nonetheless, only Gademann was capable of completing the total synthesis of Tcn-B, bringing the following answers to the β-glycosylations problem:[11,12] *a)* The Helferich's protocol (activating agent: $HgO_{(excess)}/HgBr_{2(cat)}$)[13] was used to noviosylate the C4-C13 aglycone fragment (α/β: 1/3, β : 54%), as the cyclic aglycone gave only α adducts whatever the conditions. *b)* The rhamnosylation was carried out on the macrolide, using an imidate donor (α/β: 1/4, β : 62%). Following similar strategies, Gademann also synthesized three congeners of Tcn-B: tiacumicin A,[12] and mangrolide A[14] and D.[15] In 2019, de Brabander also reported a total synthesis of mangrolide D.[16] As to our contribution, we reported two related synthetic pathways leading to the aglycone.[17] The original strategy we designed for the synthesis of its C12-C15 diene region resulted in the discovery that Pd-nanoparticles catalyze the Kumada-Corriu reaction of vinylsulfides,[18] and led us to study the Grigg's allene/alkyne cross-coupling and proposing a mechanism based on DFT calculations.[19]



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 allowed an original and selective assemblage of the three main regions of the molecule (Scheme 1). It naturally relies on our synthesis of the

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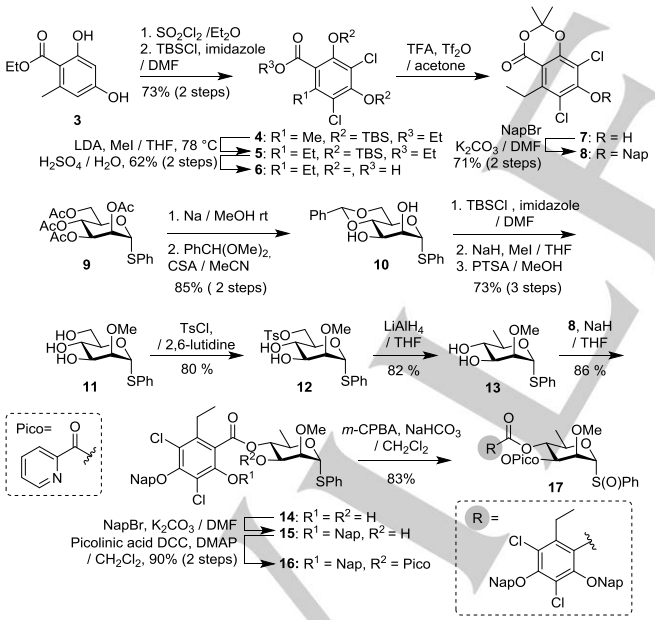
Tcn-B aglycone, whose strategy had been designed with an eye to the total synthesis. Originally, we had imagined glycosylating our aglycone sequentially, a possible viable pathway. However, we finally opted for a less traditional but more convergent retrosynthetic plan in which Tcn-B was disconnected into fragments **A**, **B** and the known **2**,[17a] equivalent in size and complexity. We chose as first move to assemble fragment **A** together with fragment **2**, then close the macrolactone, and install fragment **B** at the very end. The Suzuki coupling developed during our aglycone synthesis[17a] was considered robust enough to allow assembling fragments **2** with fragment **A**, instead of the small silylated C1-C3 fragment formerly involved,[17a] thus adding convergence. This approach reduces risks of failure since rhamnosylation conditions needed for the synthesis of **A** can be developed using the structurally simple C1-C3 fragment as the acceptor. Complete ring-size selectivity had been previously observed 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 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.[12]

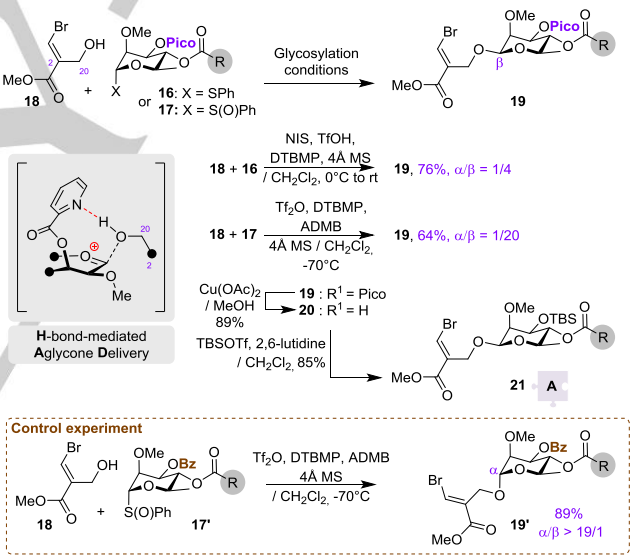
To prepare fragment **A** we considered using a *β*-selective glycosylation of acceptor **18** (Scheme 3) by the phenylthio-rhamnosyl donor **16** that bears a picoloyl group (Pico) at *O*-3 (Scheme 2).



Scheme 2. Syntheses of rhamnopyranosyl donors **16** and **17**. 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,[20] 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 were TBS-protected providing **4**. The benzylic methyl group was deprotonated with LDA then methylated giving **5**. Acidic hydrolysis led to deprotected carboxylic acid **6** that upon 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 Zemplén deacetylation and 4,6-benzylidene formation. Then **10** was selectively TBS-protected at *O*-3, methylated at *O*-2 and deprotected 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**.[11] The free phenol of **14** was protected as the Nap ether **15**, and the rhamnoside *O*-3 position was esterified with picolinic acid. This led to the expected donor **16** ready for the glycosylation of alcohol **18**[21] (Scheme 3).

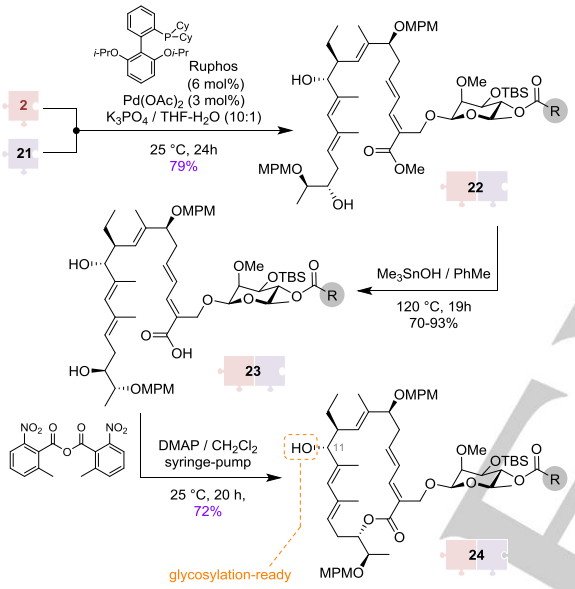


Scheme 3. Glycosylation conditions and synthesis of fragment **A**. NIS: *N*-iodosuccinimide, DTBMP: 2,6-di-terbutyl-4-methylpiridine, ADMB: 4-allyl-1,2-dimethoxybenzene.

Initial glycosylation attempts carried out in 1,2-dichloroethane with dimethyl(methylthio)sulfonium triflate, a classical promoter of H-bond-mediated Aglycone Delivery (HAD),[20] were disappointingly unsuccessful. First promising results for the coupling of donor **16** with acceptor **18** were obtained using *N*-iodosuccinimide (1 equiv/donor) and triflic acid (0.92 equiv/donor)[22] in CH_2Cl_2 at –40 °C to rt and produced **19** (76%, α/β: 1/4),[23] whose anomers were 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

acceptor **18**, DTBMP and ADMB,[24, 25] which resulted in the formation of desired glycosylated compound **19** with high facial selectivity (α/β : 1/20) and in 64% yield. To verify that this glycosylation took place through HAD, we did a control experiment using donor **17'**, an analog of **17** whose picoloyl was replaced by a benzoyl. Product **19'** was the only one formed and its α configuration indicated that the picoloyl group on donor **17** could remotely direct the nucleophilic attack to the *β*-face by forming an H-bond. The picoloyl was easily removed from **19** with $Cu(OAc)_2$, and replaced by a TBS leading to the key fragment **A** (**21**).

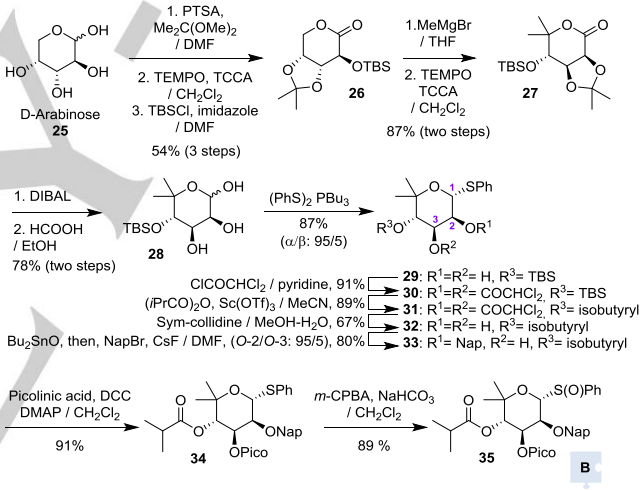
Our synthesis of aglycone fragment **2** was robust enough to be scaled up. The cross-coupling of **2** with rhamnoside **21** proceeded cleanly requiring only slight modifications of the previously used conditions.[17a] This convergent step provided ester **22** in a 79% yield (Scheme 4).



Scheme 4. Assemblage of fragments **2** and **A**, and macrolactonization. MPM: 4-Methoxyphenylmethyl.

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_3SnOH in toluene at 120 °C giving **23** with yields of 70 to 93%.[26] With seco-acid **23** in hand, we focused on the macrolactonization expecting again ring-size selectivity. However, the strict transposition of the Yamaguchi conditions[27] we had used before, led to the desired hemi-glycosylated tiacumicin B **24** with only 23% yield. The Boden-Keck's protocol[28] allowed reaching a 58% yield but **24** proved to be a mixture of two products resulting from the isomerization of the C4-C5 alkene. Finally, the Shiina's conditions[29] allowed a far cleaner and reproducible macrolactonization into **24** with 72% yield, and an isomerization minimized at 15%. Our strategy allowed keeping the OH at C11 free of protective-group throughout this synthesis so that **24** could be directly engaged in the noviosylation step.

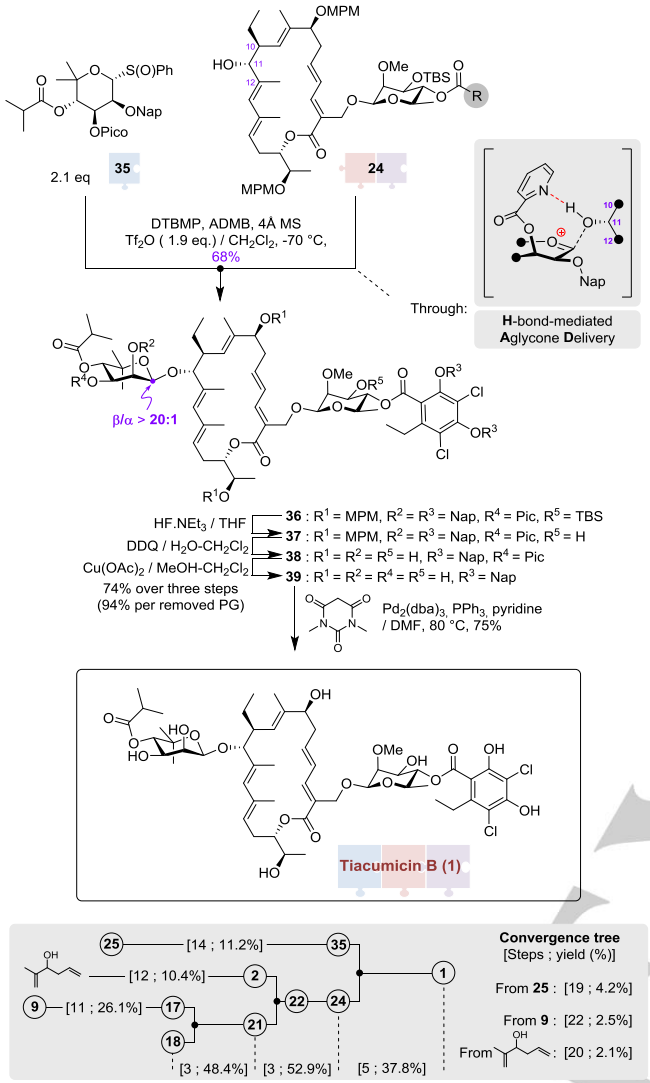
To secure good *β*-selectivity, we originally programmed to anchor the noviose using a silicon tether delivery.[30] This strategy failed, so we decided to again implement a HAD approach by installing a directing picoloyl group at *O*-3 of the sugar. The required noviosyl donor was prepared from D-arabinose **25** (Scheme 5) which 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 $(iPrCO)_2O$ and a catalytic amount of $Sc(OTf)_3$ in MeCN allowed the direct replacement of the TBS group by an isobutyrate leading to **31**.[31] 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 regioselectivity.[32]



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

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 a 72 % yield demonstrating the feasibility of this approach. Unfortunately, the glycosylation of macrolactonic acceptor **24** was unsuccessful as no adduct was detected.[12] 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_2O activation of **35** in the presence of **24**, DTBMP, ADMB/CH_2Cl_2, –70 °C) we were pleased to isolate the desired noviosylated product **33** in 68% yield, with a virtually total facial selectivity (*α*/*β* > 1/20).[33]

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 6). The 2 MPMs



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

as well as the Nap located at *O*-2 on the novioside, were readily oxidized by DDQ at 0 °C leading to tetraol **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. The removal of the Pico was cleanly carried out ($Cu(OAc)_2$/methanol-CH_2Cl_2, 0 °C) giving **39**. Importantly, this Pico group had to be removed after its neighboring Nap to prevent DDQ from forming of a 2-naphthylmethylidene bridge over *O*-2 and *O*-3 of the novioside. These three operations were carried out without intermediate purification giving **39** with an overall 74% yield (94% *per* PG). Finally, we had to address the cleavage of the two reluctant Nap groups protecting the phenol functions. Mild Pd-catalyzed hydrogenation conditions failed at being selective.[34] 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 in a good yield. The 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).

In summary, the total synthesis of tiacumicin B (**1**) was achieved, with as key steps a highly *β*-selective rhamnosylation, a Suzuki cross-coupling that allowed assembling the rhamnoside **21** with aglycone fragment **2**, a ring-size selective macrolactonization, a 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 relied 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 in addressing the biological relevance of the carbohydrate moieties of tiacumicin B or other sensitive aglycones through the preparation of a set of glycosylated analogues.

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

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[21] See the Supporting Information for its preparation.

[22] The reaction was unsuccessful with a catalytic amount of TfOH

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

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[32] A $^{3}J_{1,2}$ 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 $^{4}C_{1}$ chair but rather a $^{1}C_{4}$ 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.

[33] The α anomer could not be detected in ^{1}H NMR spectrum.

[34] 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.

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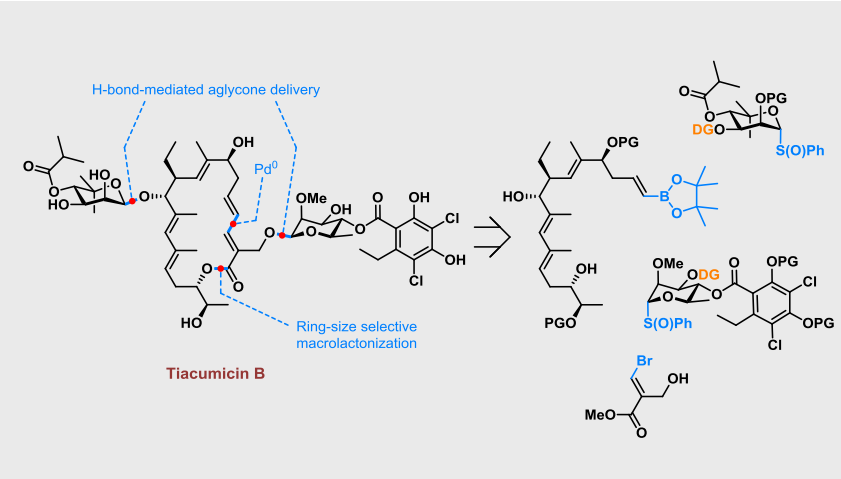

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