Full Paper

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Synthesis of *O*-linked Cyclitol Analogues of Gilvocarcin M and Antibacterial Activity

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Dedicated in honor of the 80th birthday of Prof. Barry M. Trost.

Abstract: Two unnatural regioisomeric glycosylated Gilvocarcin analogues were proposed as model compounds to study the origin behind the biosynthetic development of the Gilvocarcins, a class of bioactive *C*-aryl glycoside natural products. More specifically, the origins behind the proposed *O*- to *C*-glycoside migration in the evolution of the biosynthesis for these classes of Angucycline antibiotic natural products. For stability reasons a 5a-carbasugar motif was used to mimic the sugar portion of the molecule and of synthetic ease the proposed abiotic rearrangement move the sugar analogue along with its *O*-glycoside linkage. The two proposed regioisomeric analogues were synthesized by a regio-divergent synthetic pathway and featured a Mitsunobu-like invertive cyclictolization reaction to install the carbasugar motif. The two regioisomeric Gilvocarcin analogues were evaluated as antibiotic with Gilvocarcin M as a control. Only one of the two isomers showing weak antibiotic activity as compared to Gilvocarcin M.

Keywords: Gilvocarcin · *C*-aryl glycoside · cyclitol · carbasugar · antibacterial

Introduction

Over the years we have been interested in the use asymmetric catalysis for the *de novo* asymmetric synthesis of natural products.[1] One of the goals of this effort is to use these synthetic approaches for the medicinal chemistry study of the natural product with an emphasis on stereochemistry in the development of their SAR (aka, S-SAR).[2] These approaches have been particularly successful in the synthesis and study of carbohydrates[3,4,5] and carbohydrate based natural products,[6,7,8] via a Pd-π-allyl chemistry.[9] In this regard, we have had a long standing interest in the synthesis, biosynthesis and medicinal chemistry study around the structural space of the glycosylated angucycline natural products.[10] Of particular interest are the glycosylated variants of angucyclines with oxidatively cleaved angucycline C-rings, for example: the Jadomycins and the Gilvocarcins (Scheme 1, Figure 1).[11,12]

Both the Jadomycins and the Gilvocarcins are glycosylated Angucycline natural products that are biosynthetically derived by an oxidative cleavage of the C-ring of the Angucycline biosynthetic precursor Rabelomycin (**1**) to form a common Jadomycins and the Gilvocarcins (**2**).[12b,13] A series of decarboxylation, dehydration, aromatization and glycosylation steps converts the common intermediate **2** into the Jadomycins (**3**) and Gilvocarcins (**4**).[14] The two routes bifurcate with in the case of Jadomycins, the trapping of the aldehyde in **2** with isoleucine followed by an electrocyclic ring closure and air oxidation of the resulting hydroquinone then lactonization to give the Jadomycin C-ring. In contrast, an oxidative lactonization of the aldehyde in **2** give the C-ring lactone in the Gilvocarcins.[11,12d]

The other difference between the Gilvocarcins and the Jadomycins is that the Jadomycins are glycosylated on the phenol oxygen of the A-ring, whereas the Gilvocarcins are glycosylated para to the phenol via a *C*-aryl glycoside attachment. These observations are consistent with the biosynthetic hypothesis that *C*-aryl glycoside natural products result from a biosynthetic pathway that evolved from a pathway that originally produced a regioisomeric biosynthetic precursor.[15] Supporting this observation is the fact that the class of Angucycline natural products are replete with variant that have both *O*- and *C*-glycosylated A-rings.[16] It is often proposed that the evolutionary pressure that leads to the rearrangement of an *O*-glycoside variant to its *C*-glycoside regioisomer is that the *C*-glycoside attachment is more stable to hydrolysis.[17] The issue with *O*-glycoside instability is evident in Jadomycin B, where the hydrolysis of the digitoxose sugar to the aglycon Jadomycin A is notoriously difficult to prevent during its isolation.[12b] To address this issue, we developed a synthesis of a cyclitol variant of Jadomycin B using a Mitsunobu-like cyclitolization, where the digitoxose sugar is replaced with a 5a-carbasugar analogue.[12a] The resulting cyclitol analogue of Jadomycin B proved to be

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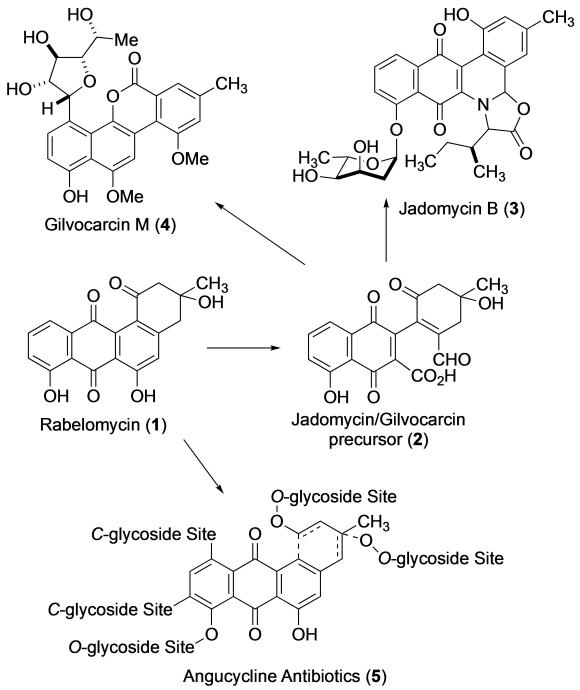


Scheme 1. Angucycline/Jadomycin/Gilvocarcin bifurcated biosynthesis.

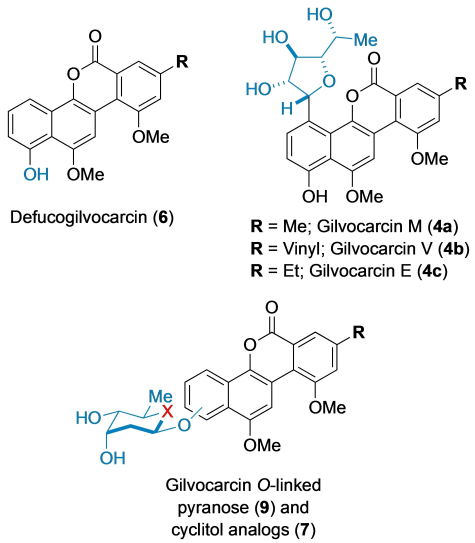


Figure 1. Gilvocarcins and their analogues.

significantly more stable to acid hydrolysis. Similarly, Yu developed a mild Mitsunobu-type glycosylation that was able to prepare the highly acid sensitive Jadomycin B.[18]

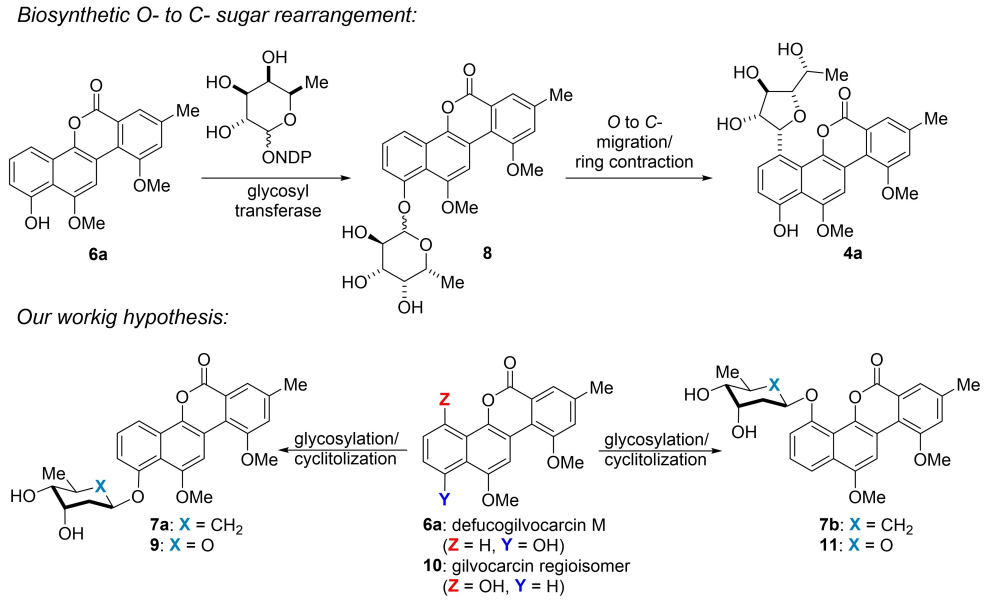
Thus, it is reasonable to assume that in the evolutionary history of the biosynthesis of the Gilvocarcins (**4a-c**) there may have been time when it produced an A-ring *O*-glycoside like the Jadomycins and that sugar might have been a digitoxose (Fig. 1).[19] To explore the question of whether the *O*- to *C*-sugar migration occurs in the evolution in the Gilvocarcin biosynthesis to simply improve stability or to improve potency, we proposed to synthesize and study two regioisomeric A-ring *O*-glycoside analogues of Gilvocarcin M (**7**).[20] Our previous issues with instability of the *O*-glycosides (*e.g.*, Jadomycins) inspired us to also prepare cyclitol variants (**9**) of the pyranose sugars, which should be less resistant to hydrolysis. While the Gilvocarcins have received a lot of attention for their anticancer activity (*e.g.*, topoisomerase mediated DNA cleavage for Gilvocarcin V),[21] if there were an evolutionary pressure based upon an increase in biological activity behind to the *O*- to *C*-migration that improved activity would have been against bacteria and not cancer cells. Recently, Rohr showed that biosynthetically engineered Gilvocarcin analogs with varied sugar stereochemistry and substitutions retained anticancer activity.[22] Accordingly, one might expect that if a digitoxose variant of the Gilvocarcins was ever produced, it would have biological activity (Scheme 2).

Results and Discussions

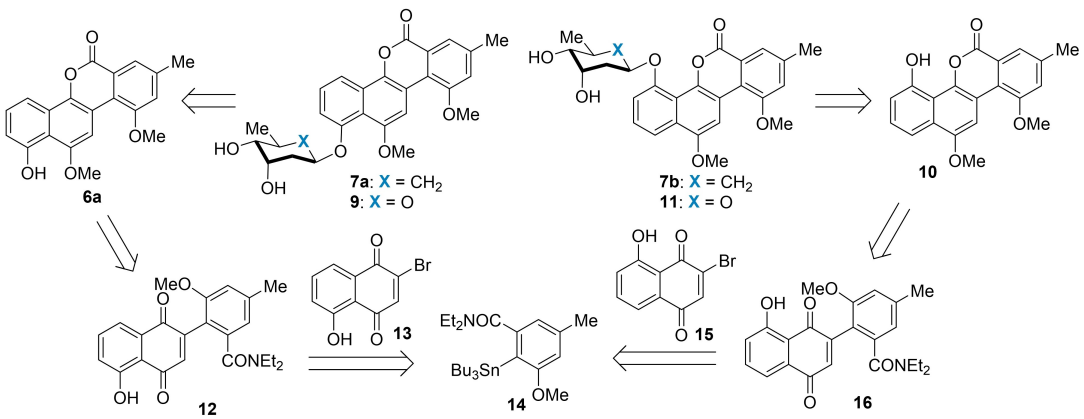
Retrosynthetically we envision the two regioisomeric Gilvocarcin analogues, the *O*-glycosides **9** and **11** as well as their cyclitol analogues **7a** and **7b**, as coming from the Gilvocarcin aglycon **6a** or its regioisomeric phenol **10** (Scheme 3). Both the Gilvocarcin aglycon **6a** and its isomer **10** could in turn come from the appropriate regioisomeric biaryl napthraquinones **12** and **16**. The two regioisomeric anthraquinones **12** and **16** would come from a Stille-type cross coupling between stannane **14** and the two regioisomeric bromonapthraquinones **13** and **15**.[22]

We disbanded our attempts aimed at the synthesis of *O*-glycoside analogues (**17**), when we ran into difficulty with the glycosylation of the Gilvocarin aglycon **6a** (Scheme 4). All attempt we made at glycosylating the phenol of **6a** under our Pd-glycosylation,[23] traditional glycosylation,[24] or Mitsunobu-type glycosylation[20] were unsuccessful. More specifically, a Pd-glycosylation reaction between **6a** and Pd-glycosyl-donor **18a** failed. Similarly, our attempts at glycosylation of **6a** under the Schmidt-type glycosylation conditions with trichloroacetimidate**18b** and **18c**, were unsuccessful. Even the mild Mitsunobu-type glycosylation reaction developed by Yu and co-workers failed to give the desired products from the reaction with **6a** and anomeric alcohols **18d** and **18e**.[20] We associated the difficulties of these approaches to the instability of the glycosidic linkage in **17** and thus decided to pursue the synthesis of the more stable cyclitol Gilvocarin analogues **7a** and **7b**.

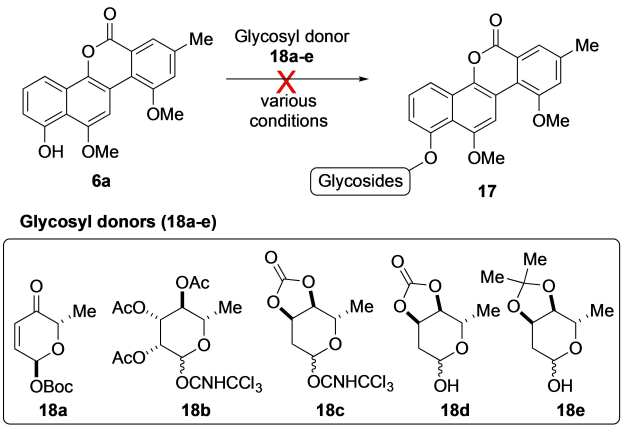
In response to our unsuccessful efforts at synthesizing the pyranose glycosides **17**, we turned our attention towards the synthesis of their 5a-carbasugar analogues **7a** and **7b**, which in turn required the synthesis of cyclitol donor **25**, with a free alcohol at *C*-1 with α-stereochemistry. The approach mimics our *de novo* asymmetric approach to digitoxose from



Scheme 2. Biosynthetic sugar rearrangement and our approach to *O*-glycosyl/cyclitol analogues.

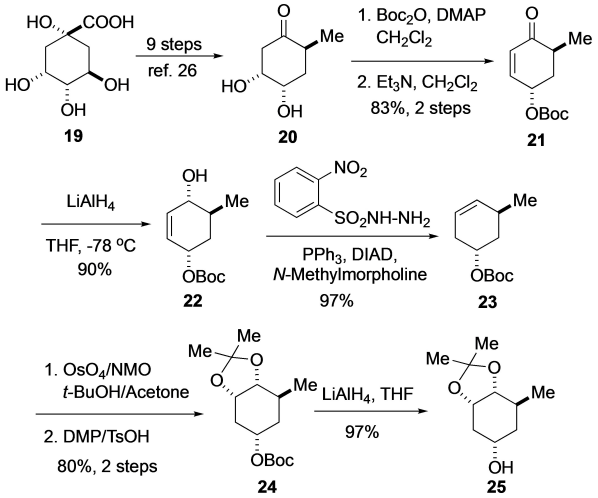


Scheme 3. Retrosynthetic analysis for regioisomeric *O*-linked cyclitol analogues.



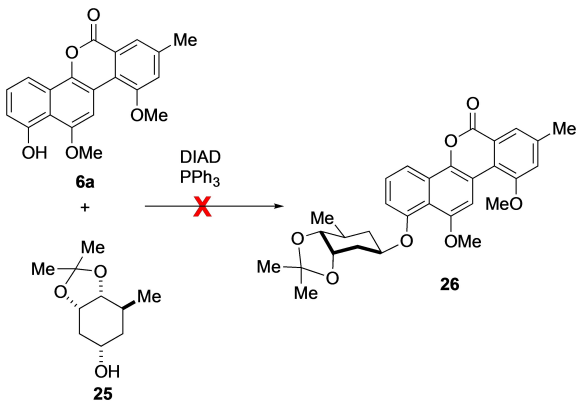
Scheme 4. Attempted glycosylation of defucogilvocarcin M (**6a**).

acetylfuran.[25] The α-stereochemistry is required as we envision upon assembling the glycosidic bond by means of an invertive Mitsunobu-type cyclitolization. Our synthesis of the desired cyclitol donor **25** begins with ketodiol **20**, which was prepared in 9 steps from Quinic acid (**19**) (Scheme 5).[26] A 2-step carbonate formation/elimination procedure converted the diol **20** into the enone **21**. A selective 1,2-reduction of **21** with $LiAlH_4$ at low temperature gave **22** as a single allylic alcohol diastereomer. The allylic alcohol **22** reacted under the Myers reductive rearrangement protocol to give alkene **23** as a single diastereomer.[27] A highly diastereoselective Upjohn dihydroxylation[28] of **23** followed by acetonation of the resulting diol gave acetonide **24**. Finally, $LiAlH_4$ was used to remove the Boc-protecting group to give the desired Mitsunobu cyclitolization donor **25**.



Scheme 5. Asymmetric synthesis of D-digitoxose cyclitol donor **25.**

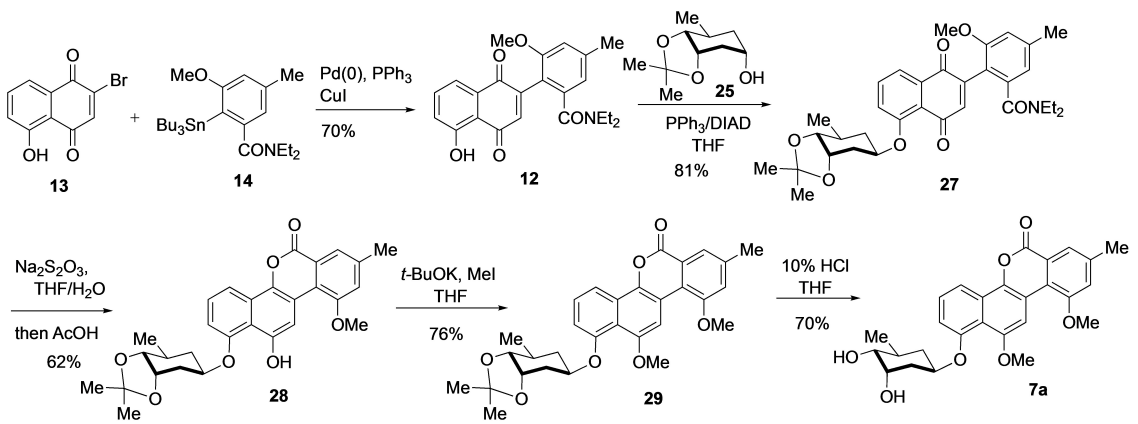
Unfortunately, our attempts aimed at the synthesis of cyclitol analogues **26** under the mild Mitsunobu-type cyclitolization protocol, were unsuccessful (Scheme 6). Specifically, when exposed Gilvocarcin aglycon **6a** to our typical Mitsunobu-type cyclitolization conditions with alcohol **25**, no cyclitol coupling products were detected. We attributed this result to the poor reactivity of the electron rich phenol in **6a**. In fact, we had seen similar issues with poor Mitsunobu reactivity in our Jadomycin A/B synthesis.[12a] Building upon our experience gained in our Jadomycin synthesis, we decided to explore the use of electron poor phenols for use in the Mitsunobu synthesis, which could be converted into the requisite aglycon motif (Scheme 7). Previously Martin had shown that the use of electron withdrawing groups on carboxylic acid can have a profound effect on their ability to participate as the nucleophile in Mitsunobu esterifications.[29]



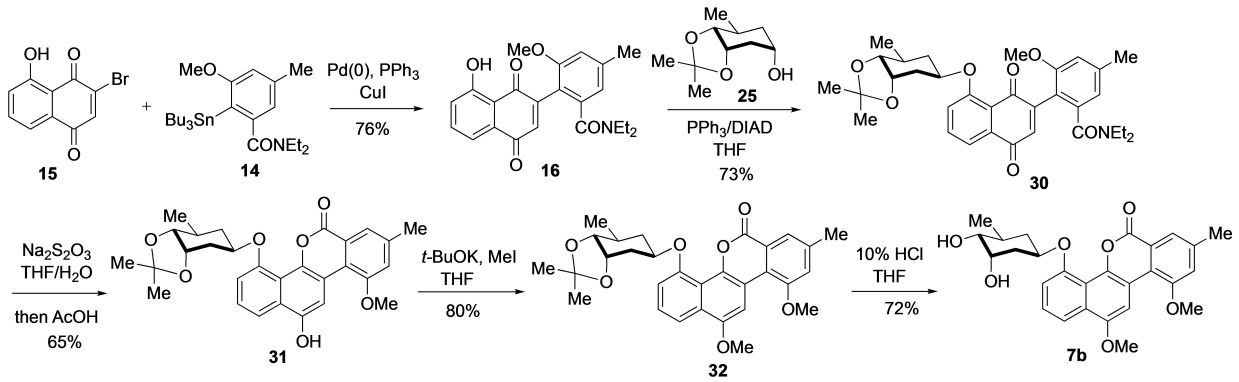
Scheme 6. Attempted cyclitolization of Defucogilvocarcin M (**6a**).

This synthetic misfortune led us to the use of the electron deficient phenol in napthraquinone **12** as the nucleophilic coupling partner (Scheme 7). The synthesis of **12** was straightforward involving a copper iodide/Pd(0) variant of the Stille-coupling reaction between bromide **13** and stannane **14**, affording the hydroxynapthaquinone **12** in a satisfying 70% yield.[23] With the desired phenol **12** in hand, we were delighted to find that it performed admirably in the Mitsunobu-cyclitolization[12a] with cyclitol-donor **25**. Thus, under our optimized conditions the Mitsunobu-cyclitolization between coupling partners **12** and **25** afforded the cyclitol product **27** in excellent 81% yield. The requisite Gilvocarcin lactone ring was next installed by a 2-step napthaquinone to napthaquinol reduction followed by an acid catalyzed lactonization to give the tetracyclic aglycon precursor in 62% yield. A final aglycon adjustment involved methylation of the B-ring phenol, with KO*t*-Bu and MeI, to give the protected analogue **29**. All that remained to arrive at the desired analogue was an acetonide deprotection, with aqueous HCl to give the cyclitol analogue of our proposed biosynthetic precursor **7a**, which occurred in a 70% yield.

Gratifyingly, an analogue five step procedure gave the desired regioisomeric cyclitol analogue **7b** (Scheme 8). The synthesis began with a similar copper iodide variant of the Stille Pd-catalyzed cross-coupling reaction between the regioi-



Scheme 7. Synthesis of *O*-linked cyclitol analogues of Gilvocarcin M (**7a**).

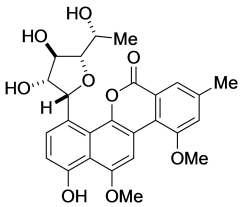
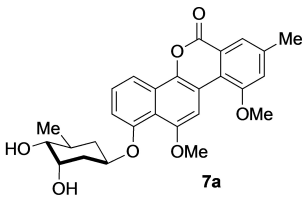
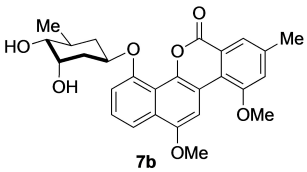


Scheme 8. Synthesis of regioisomeric *O*-linked cyclitol analogues of Gilvocarcin M (**7b**).

someric bromide **15** and stannane **14** to give the regioisomeric hydroxynapthaquinone **16** in a similar yield (76%). The regioisomeric phenol on napthaquinone **16** reacted similarly in the Mitsunobu-cyclitolization with cyclitol-donor **25** to give the cyclitol product **30** (73% yield). Analogously the lactone ring was installed by a 2-step reduction to a napthaquinol followed by an acid catalyzed lactonization to give the tetracyclic aglycon precursor **31** (65% yield). The regioisomeric phenol in **31** was then methylated with KO*t*-Bu and MeI to give the protected analogue **32**. Finally, the acetonide was removed with aqueous HCl to give the proposed regiosiomeric cyclitol analogue **7b** in a 72% yield.

With the two regioisomeric cyclitol analogues in hand we next turned to their evaluation as antibiotics. Previously it had been reported that Gilvocarcin M had inhibitory activity against Gram-positive bacteria methicillin-sensitive *S. aureus* (MSSA) (Table 1).[30] Using a standard MIC assay we evaluated regioisomer **7a** and **7b** against a commonly used MSSA lab strain HG003 with Gilvocarcin M as a control.[31] While the Gilvocarcins are of interest medically for their anticancer activity, the selection processes that guided the development of the biosynthesis of the Gilvocarcins must have been based upon their antibacterial activity. Thus, we decided to evaluate them as antibiotics against HG003. In our assay, Gilvocarcin M was found to have a minimum inhibitory activity against HG003 lab strain at 60 μg/mL. Interestingly, we were not able to find an MIC activity for the regioisomer **7a**, as solubility issues arose at concentrations great than 150 μg/mL. In contrast, a significantly reduced but measurable activity (150 μg/mL) was found for the analogue **7b** with the cyclitol ring in the position before *O*- to *C*-glycoside rearrangement. This suggest that the position of the sugar in the rearrangement product was a significant factor in the biosynthetic outcome form the *O*-linkage to *C*-glycoside migration that of the evolutionary process that resulted in the synthesis of Gilvocarcin M.

Table 1. MIC activities against methicillin-sensitive *S. aureus* (MSSA).

Compound	MIC (μg/mL)
 Gilvocarcin M (**4a**)	60
 **7a**	>150
 **7b**	150

Conclusion

The synthesis of a cyclitol analogues of a proposed biosynthetic precursor **7a** and its regioisomer **7b** was developed. The synthetic approach involved the use of a novel Mitsunobu-type cyclitolization reaction to install the desired cyclitol analogue of the digitoxose ring. The Gilvocarcin analogues we evaluated as antibacterial agents with Gilvocarcin M used as a control. Both cyclitol analogues exhibited reduced antibacterial activity as compared to Gilvocarcin M. The reduced activity of the regioisomer **7a** (the cyclitol analogue of the proposed biosynthetic precursor **9**) to **7b** is suggestive that if *O*-glycoside **9** was an intermediate on the evolutionary path of the biosynthesis of the Gilvocarcins the *O*- to *C*-migration was driven by an increase in antibacterial

activity. Further studies along these lines are ongoing and will be reported in due course.

Supporting Information

Experimental details, characterization data, and ^{1}H, and ^{13}C NMR spectra for all new compounds (PDF)

Acknowledgements

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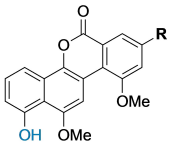
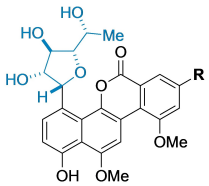
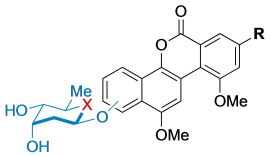


Defucogilvocarcin (**6**)



R = Me; Gilvocarcin M (**4a**)
R = Vinyl; Gilvocarcin V (**4b**)
R = Et; Gilvocarcin E (**4c**)



Gilvocarcin *O*-linked pyranose (**9**) and cyclitol analogs (**7**)

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