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# A Synthesis Strategy for the Production of a Macrolactone of Gulmirecin A via a Ni(0)-Mediated Reductive Cyclization Reaction

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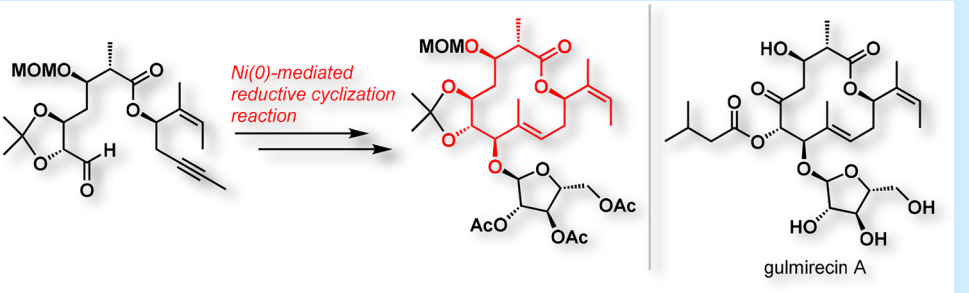


**ABSTRACT:** A synthesis strategy for the production of a key synthetic intermediate of gulmirecin A was described. The key reaction in the preparation of the 12-membered macrolactone is the Ni(0)-mediated reductive cyclization reaction of ynal using an *N*-heterocyclic carbene ligand and silane reductant. In addition, the $\alpha$-selective glycosylation reaction of the macrolactone was performed to demonstrate the synthesis of gulmirecin and disciformycin precursors.

Since the discovery of antibiotics and vaccines, the number of deaths due to infectious diseases has drastically decreased. However, the frequent prescription and unregulated usage of antibiotics against infectious diseases have permitted drug-resistant bacterial pathogens to spread rapidly.[1] According to the antibiotic resistance threats reported by the U.S. Centers for Disease Control and Prevention in 2019, more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, causing 35,000 deaths.[2] Hence, the development of new antibacterial drugs with novel mechanisms of action is urgently needed to avoid cross-resistance with approved drugs.

In 2014, gulmirecin A (**1**) and B (**2**) were isolated from *Pyxidicoccus fallax* HKI 727 as potential antimicrobial agents against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) (Figure 1).[3] In the same year, disciformycin A (**3**) and B (**4**) were isolated from *Pyxidicoccus fallax* AndGT8 for similar use as potential antimicrobial agents.[4]

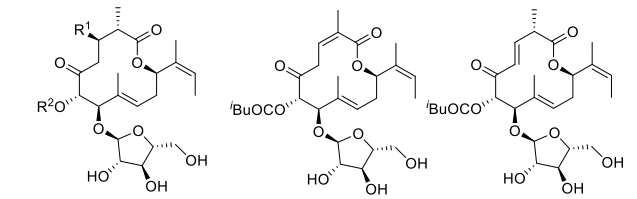


**Figure 1.** Structures of gulmirecins and disciformycins.

These natural products **1**−**4** had no cytotoxic effects on human cells at concentrations of up to 10 $\mu$M. Because these natural products have excellent properties for avoiding cross-resistance with methicillin and vancomycin, they have the potential to become effective antibacterial leads with activity against multidrug-resistant bacteria although their targets have not yet been clarified. The total synthesis of disciformycins has been accomplished by the groups of Müller[5] and Fürstner,[6] and synthesis studies of disciformycin B and gulmirecin B have also been reported by the groups of Kirschning[7] and Maier,[8] respectively. Despite considerable effort to synthesize gulmirecins and disciformycins, no studies of the synthesis of their analogues of gulmirecin A have been reported, and their structure−activity relationships must still be elucidated.

Structurally, gulmirecins and disciformycins are closely related but differ in the region of the C2−C4 positions and in the presence or absence of an isovaleryl group attached to the hydroxy group at the C6 position. The group of Kirschning proposed a biosynthetic relationship between gulmirecins and disciformycins (Scheme 1).[7] First, the thioesterase on the polyketide synthase GulF, which binds substrate **5**, produces the macrolactone and subsequent oxidation at the C6 position

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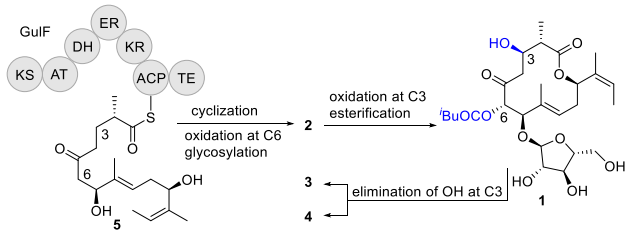
**Scheme 1. Proposed Biosynthetic Relationship between Gulmirecins and Disciformycins**[a]

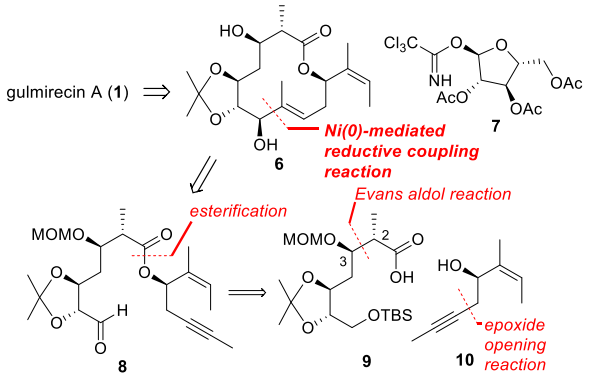



[a]KS = β-ketoacyl synthase, AT = acyl transferase, DH = dehydratase, ER = enoyl reductase, KR = ketoreductase, ACP = acyl carrier protein, TE = thioesterase.

by Cyp450 gives gulmirecin B (**2**). Second, oxidation at the C3 position and the esterification of the hydroxy group at the C6 position of **2** result in gulmirecin A (**1**). Finally, the elimination of the hydroxy group at the C3 position can produce disciformycin A (**3**) and B (**4**). This proposed biosynthetic pathway motivated the development of a standardized synthesis route applicable to this class of natural products using a gulmirecin A-type macrolactone as a key synthetic intermediate (**6**). Here, the synthesis of a gulmirecin A-type macrolactone through a Ni(0)-mediated reductive cyclization reaction is reported as an example of a novel method for preparing macrolides.

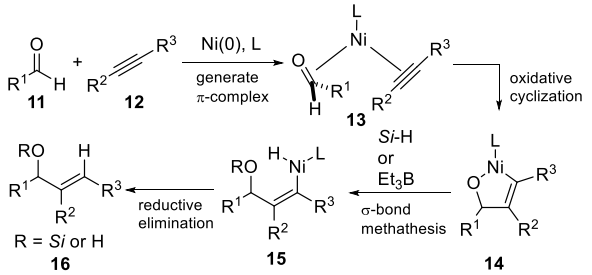
A retrosynthetic analysis of **1** is shown in Scheme 2. The final stage of the synthesis was planned to include the

**Scheme 2. Retrosynthetic Analysis of Gulmirecin A (1)**




introduction of a D-arabinose moiety (using trichloroacetimidate **7**) and an isovaleryl group into the macrolactone and the oxidation of the hydroxy group at the C5 position. The 12-membered macrolactone **6** was to be synthesized via a Ni(0)-catalyzed reductive coupling reaction[9] involving ynal **8**. In the Ni(0)-catalyzed reductive coupling reaction reported by the group of Montgomery, an alkyne and an aldehyde react over a Ni(0) catalyst with phosphine or an *N*-heterocyclic carbene as a ligand to give an allyl alcohol. The proposed reaction mechanism is shown in Scheme 3. Initially, the ligand and Ni(0) form a metal complex (**13**), which forms a π-bonded complex with the aldehyde and alkyne. The oxidative cyclization of this complex produces five-membered metallacycle intermediate **14**. Subsequently, σ bond metathesis of the nickel and oxygen bonds proceeds with the use of a reducing agent such as silane or borane to give **15**. Finally, the reductive elimination of nickel gives the allyl alcohol or the corresponding silyl ether with the regeneration of the Ni(0)

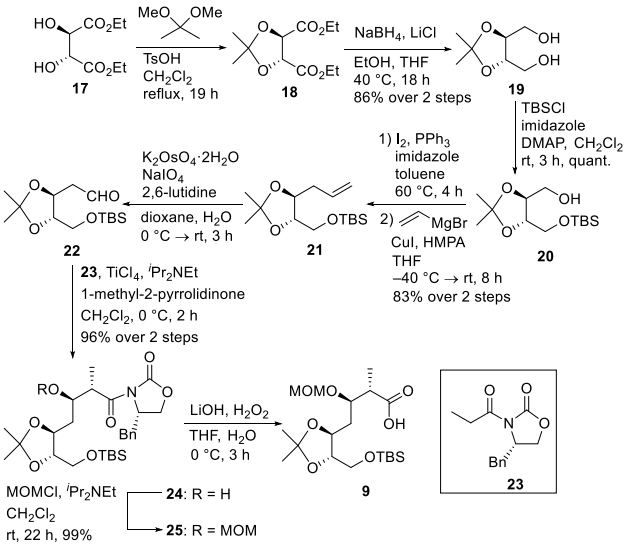
**Scheme 3. Ni(0)-Mediated Reductive Coupling Reaction**




catalyst. According to previous research, the regioselectivity of the oxidative cyclization can be controlled by the size of the ligand used.[9] This reaction is useful for the synthesis of natural products because aldehydes and alkynes are easily synthesized, and it can be applied to intramolecular reactions when ynal is the substrate.[10] It was assumed that the reductive coupling with a Ni(0) catalyst described above would be useful for the synthesis of intermediate **6**. Ynal **8** was removed from carboxylic acid **9** and alcohol **10** via esterification. Carboxylic acid **9** would be produced by an Evans aldol reaction establishing the stereochemistry of the methyl group at the C2 position and the hydroxy group at the C3 position. Alcohol **10** would be synthesized by an epoxide-opening reaction with 1-propyne.

The synthesis commenced with the preparation of **9** (Scheme 4). The diol of commercially available diethyl L-

**Scheme 4. Synthesis of Carboxylic Acid 9**




(+)-tartrate (**17**) was protected by forming an acetonide, which was followed by the reduction of the diester of **18** to give the corresponding diol **19** in 86% yield in two steps. The monoprotection of the resulting hydroxy groups by a TBS group gave alcohol **20**. The Appel reaction of **20** was conducted to afford the corresponding iodide, which was reacted with vinylmagnesium bromide in the presence of CuI to give the alkene **21** in 83% yield in two steps. Although the olefin of **21** was oxidized by treatment with $O_3$, the desired aldehyde **22** was not obtained because of the decomposition of the substrate. The oxidative cleavage of the olefin by $OsO_4$–$NaIO_4$ with 2,6-lutidine[11] produced aldehyde **22** in quantitative yield. In the case of the Evans aldol reaction between **22**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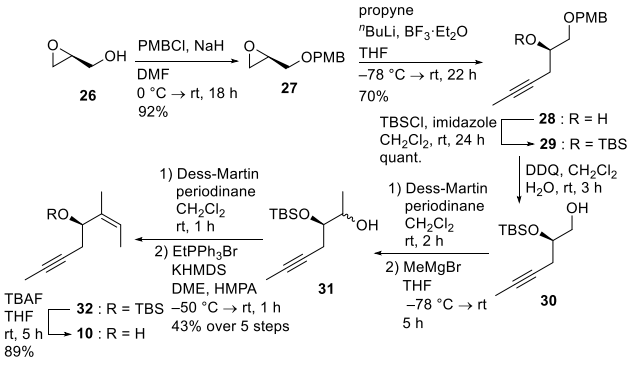
and oxazolidinone **23** with $^{n}Bu_2BOTf$ as a Lewis acid, the desired alcohol **24** was not obtained. On the other hand, the $TiCl_4$-mediated aldol reaction[12] proceeded smoothly to give the desired alcohol **24** stereoselectively in 96% yield in two steps. The protection of the resulting alcohol of **24** by a MOM group was followed by the hydrolysis of the oxazolidinone, affording carboxylic acid **9**.

The synthesis of alcohol **10** is shown in Scheme 5. (*S*)-Glycidol (**26**) was protected with a PMB group in 92% yield.

**Scheme 5. Synthesis of Alcohol 10**

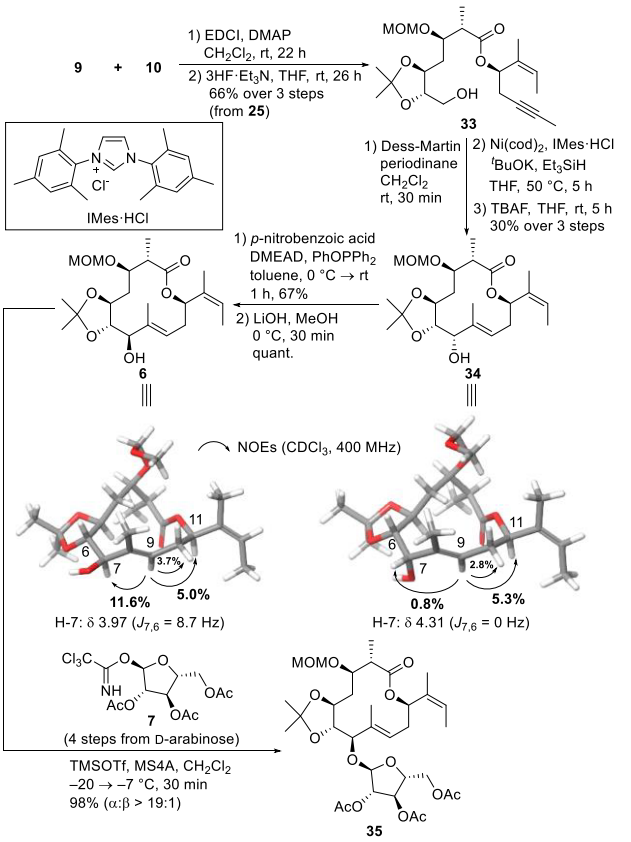



The epoxide-opening reaction of **27** with lithium methylacetylide was promoted by $BF_3{\cdot}OEt_2$ to give **28** in 70% yield, and the resulting hydroxy group of **28** was protected by a TBS group to obtain alkyne **29**. The removal of the PMB group gave alcohol **30**. The Dess-Martin oxidation of **30** was followed by the addition of methylmagnesium bromide to the aldehyde to give alcohol **31**. The resulting hydroxy group was oxidized by the Dess-Martin periodinane to afford a ketone. Then, the desired *Z*-olefin was produced by the Wittig reaction with ethyl triphenylphosphonium bromide to give **32**. Finally, the TBS group was deprotected by TBAF to afford the desired alcohol **10**. The stereochemistry of **10** was determined by comparing the specific rotation with a literature value.[6]

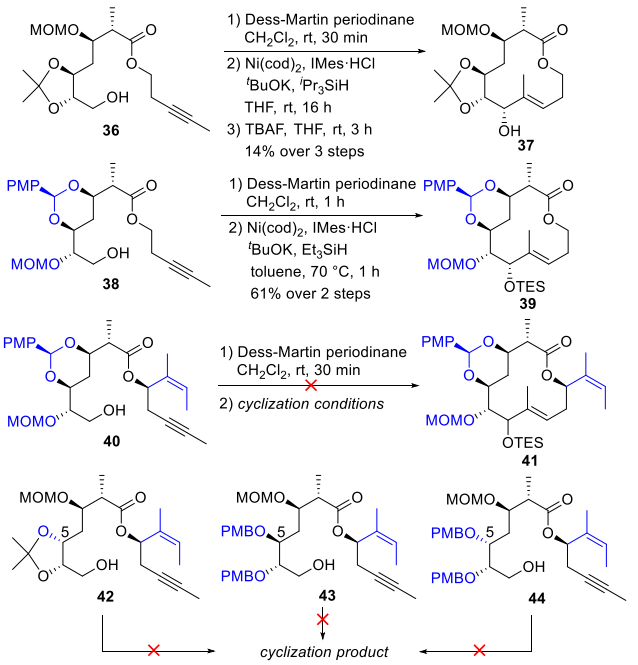
The condensation of **9** with **10** was conducted with 1-(3-(dimethylamino) propyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP in $CH_2Cl_2$ to afford the desired ester, and the subsequent deprotection of the TBS group of the ester by $3HF{\cdot}Et_3N$ gave alcohol **33** in 66% yield in three steps starting from **25** (Scheme 6). The oxidation of the hydroxy group of **33** was conducted under various conditions to obtain ynal **8**, which is a precursor of the cyclization (see SI). However, the desired aldehyde was not obtained because of an intermolecular aldol reaction or polymerization via the hydration of the aldehyde. After extensive optimization, a procedure for obtaining **8** by Dess-Martin oxidation without an aqueous workup was discovered. The synthesis route for **8** was established and applied to the synthesis of various cyclization precursors, which are described later in Scheme 7.

With the cyclization precursor **8** in hand, the Ni(0)-mediated reductive cyclization reaction was investigated using the conditions developed by the group of Montgomery to promote the *endo*-selective reductive cyclization.[9] Namely, **8** was reacted with bis(1,5-cyclooctadiene)nickel ($Ni(cod)_2$) in the presence of 1,3-dimesitylimidazolium chloride (IMes·HCl), potassium *tert*-butoxide ($^{t}$BuOK), and triethylsilane to successfully produce the desired macrolactone **34** in 30% yield in three steps starting from **33**. The macrolactone was obtained as a single diastereomer, and no regioisomers were obtained.

**Scheme 6. Synthesis of the Key Synthetic Intermediate 6 and Glycoside 35**




**Scheme 7. Scope and Limitation of Ni(0)-Mediated Reductive Cyclization Reaction**




Therefore, the reaction proceeded stereoselectively as expected. When other ligands (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), and $Me_3P$) and reductants ($^{i}Pr_3SiH$, $Ph_3SiH$ and $Et_3B$) were employed no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cyclization products were obtained (see Supporting Information (SI)).

To examine the effects of the structure of the cyclization precursor on the Ni(0)-mediated reductive cyclization reaction, **36** and **38** with a simplified side chain were synthesized (Scheme 7). The reductive cyclization reaction of the aldehyde, which was obtained by the Dess-Martin oxidation of **36**, in the presence of $Ni(cod)_2$, IMes·HCl, $^t$BuOK, and $^i$Pr$_3$SiH in THF was followed by the deprotection of the TIPS group to afford macrolactone **37** in 14% yield in three steps. Interestingly, cyclization reaction with the ynal derived from **38**, which has a *p*-methoxybenzylidene acetal group, proceeded smoothly to afford **39** in 61% yield as a single diastereomer.[13] Given the importance of the protecting group, the cyclization reaction of **40**, which has the same protection mode as **38**, was examined. Unexpectedly, the cyclization of the aldehyde derived from **40** gave no products. The possibility of cyclization is assumed to depend on the conformation of the precursor ynal, which is affected by the side chain and the mode of protection. To gain further insight into the cyclization, **42**, which has a different stereochemistry than **33** at the C5 position; **43**, which has a flexible conformation due to the absence of a cyclic protecting group; and its stereoisomer **44** were synthesized. The cyclization reactions of the aldehydes prepared from **42**−**44** gave no products. These results suggest that the reductive coupling reaction in the presence of Ni(0) proceeds only in a specific conformation.

With macrolactone **34** in hand, the stereoinversion of the hydroxy group at the C7 position of **34** was examined. Initially, the stereoinversion was conducted by an oxidation−reduction sequence at the C7 position or an $S_N2$ reaction with various nucleophiles to mesylate **34**; however, the desired inversion product was not obtained. Fortunately, the Mitsunobu reaction with *p*-nitrobenzoic acid, bis(2-methoxyethyl) azodicarboxylate (DMEAD), and $PhOPPh_2$[14] in toluene proceeded smoothly to give a 67% yield. This reaction did not proceed when $PPh_3$ or $Bu_3P$ was used instead of $PhOPPh_2$. The hydrolyzation of the corresponding *p*-nitrobenzoate by LiOH in MeOH proceeded smoothly to afford the desired macrolactone **6**. The relative configuration at the C7 position, which was obtained by the cyclization and Mitsunobu reactions, was determined from the NOE correlation between H-7 and H-9 in Scheme 6. To demonstrate the possibility of the total synthesis, the glycosylation reaction of **6** was performed. Macrolactone **6** was reacted with trichloroacetimidate **7**, which was synthesized from D-arabinose in four steps,[15] in the presence of TMSOTf and MS4A in $CH_2Cl_2$ to produce **35** in 98% yield with high $\alpha$-stereoselectivity ($\alpha/\beta$ > 19:1). Removal of the MOM and/or isopropyridene groups of **35** was briefly investigated. However, these protecting groups were resistant to the conditions using camphorsulfonic acid (MeOH, rt to reflux) or trifluoroacetic acid ($CH_2Cl_2$, rt. to reflux). The use of more harsh conditions (i.e., TMSOTf, $CH_2Cl_2$, 0 °C to rt) gave a complex mixture of products.

In conclusion, to develop a new synthesis route for the novel macrolide glycosides **1**−**4**, synthesis studies of the key synthetic intermediate **6** were performed. The key to the preparation of the 12-membered macrolactone was a Ni(0)-mediated reductive coupling reaction using easily accessible fragments. In addition, various cyclization precursors were synthesized to study the scope and limitation of the substrate. The key synthetic intermediate could be obtained from commercially available simple materials in an overall chemical yield of 8.1% via the longest linear sequence of 16 steps. Furthermore, the $\alpha$-selective glycosylation of **6** and **7** proceeded with high stereoselectivity in efficient yields. Studies of the total syntheses of natural products and their analogues using this strategy are ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00665.

Detailed experimental procedures and characterization of new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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