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Total syntheses of *ent*-aogacillin A and aogacillin B

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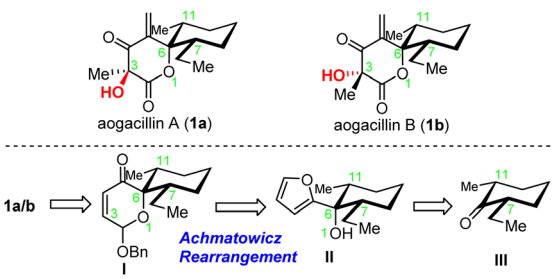
Aogacillins A and B, circumventors of arbekacin resistance in MRSA, possess a densely oxidized spirolactone moiety and an electron deficient terminal exocyclic double bond. This represents a challenging target for total synthesis. Herein, the evolution of a successful strategy for the total synthesis of *ent*-aogacillin A and aogacillin B is described. Although the spirocyclic skeleton could be efficiently constructed by the Achmatowicz rearrangement-based strategy, the elaboration of the dihydropyranone moiety to the fully functionalized lactone of aogacillins was not successful. A new strategy is proposed and successfully implemented, which features allylic C–H oxidation and a one-pot sequential aldol reaction and lactonization. This enables us to achieve the first and asymmetric total synthesis of aogacillin B and *ent*-aogacillin A in 7 steps.

Introduction

Aogacillins A and B (**1a** and **1b**, Scheme 1) were isolated by Shiomi and co-workers in 2013 from a culture broth of *Simplicillium* sp. FKI-5985 and have been found to be capable of overcoming arbekacin (ABK) resistance in methicillin-resistant *Straphylococcus aureus* (MRSA).[1] Arbekacin, a clinically used, potent antibiotic for the treatment of infections caused primarily by multi-resistant bacteria such as MRSA, has recently begun to suffer from much resistance, possibly due to phosphorylation or acetylation by bacterial aminoglycoside-modifying enzymes.[2] Aogacillins were found to inhibit the growth of MRSA with a MIC value of 2.0 μg mL^{-1} and considerably reduce the MIC value of arbekacin against arbekacin-resistant MRSA from 256 μg mL^{-1} to 8 μg mL^{-1}, which suggested that aogacillins could be specific circumventors for ABK-resistant MRSA. It was also reported that aogacillins could be used to prepare drugs for treating renal insufficiency,[3] renal carcinoma,[4] breast cancer,[5] Alzheimer's disease[6] and type-2 diabetes.[7] Therefore, they hold great potential for clinical applications. Structurally, aogacillins represent an unusual δ-lactone with a spiro-fused 2-ethyl-6-methylcyclohexane, and their highly dense functionalities (especially the continuous high oxidation states) on the δ-lactone pose a major challenge for their chemical synthesis. The terminal *exo*-cyclic alkene conjugated with the carbonyl, acting as a Michael acceptor, also makes these compounds unstable. Aogacillin A (**1a**) differs structurally from aogacillin B (**1b**) only at C3 stereochemistry, which makes their separation very difficult as evident from NMR spectra of **1b** containing residues from those of **1a**. The total syntheses of both aogacillins A and B have not been reported so far. Herein, we describe our efforts to achieve the first total synthesis of aogacillin B and the enantiomer of aogacillin A.



Scheme 1 Aogacillins A and B and retrosynthetic analysis.

Results and discussion

Our original retrosynthetic analysis was proposed in 2013 and hinged on the Achmatowicz rearrangement as depicted in Scheme 1. The fully functionalized δ-lactone of aogacillins A and B could be generated from the dihydropyranone acetal moiety of intermediate **I**, which was derived from the Achmatowicz rearrangement of furfuryl alcohol **II**. The addition of 2-lithiofuran to *cis*-2-ethyl-6-methyl-cyclohexanone delivered **II** as the substrate for the Achmatowicz rearrangement. It should be noted that the Achmatowicz rearrangement has been applied as

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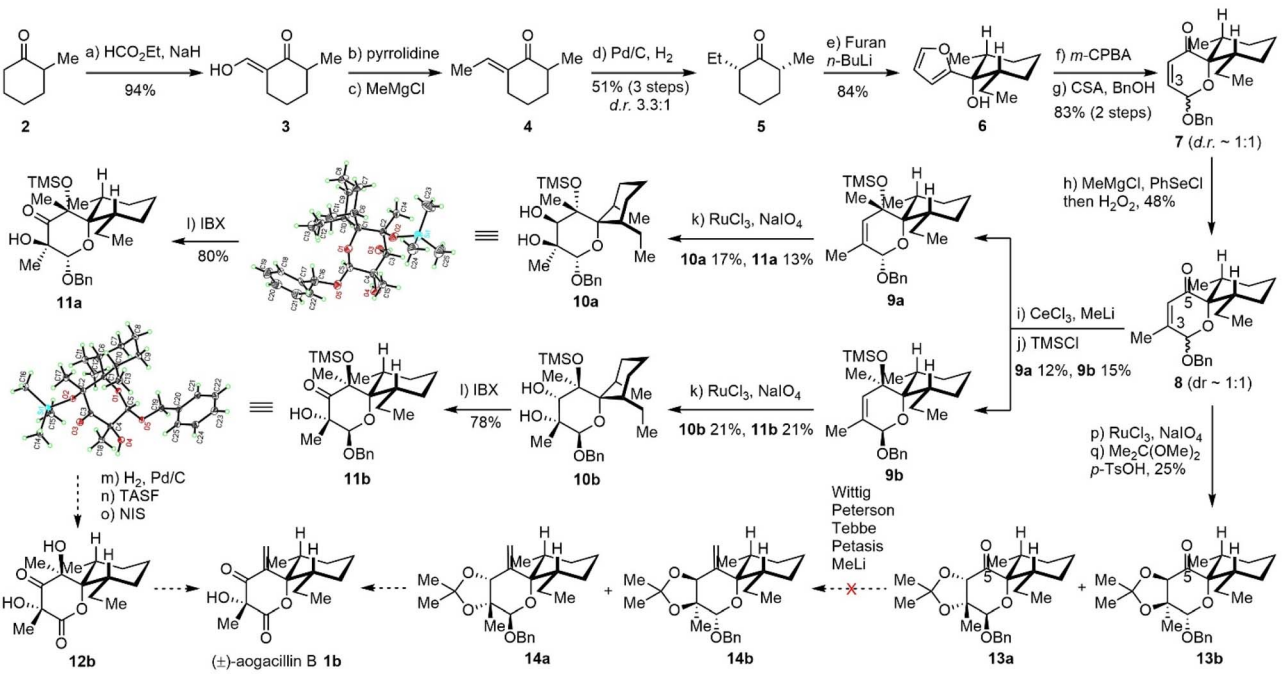
the key strategic transformation in the total syntheses of various natural products containing tetrahydropyrans,[8] spiroketals,[9] and oxa-bridged bicycles[10] and we have extensive experience in the exploitation of Achmatowicz rearrangement.

As shown in Scheme 2, our synthesis commenced with the preparation of *cis*-2-ethyl-6-methyl-cyclohexanone **5**. Claisen condensation of ethyl formate with commercially available 2-methyl cyclohexanone **2** (ref. 11) was followed by enamine formation and the Benary reaction[12] to deliver *E*-ethylidene ketone **4**.[13] Hydrogenation with Pd/C in ethyl acetate gave the desired *cis* product with high yield and good diastereoselectivity. This scalable four-step-one-purification sequence provided *cis*-2-ethyl-6-methyl-cyclohexanone **5** (ref. 14) in multigram quantities in a single batch. Addition of lithiated furan to **5** afforded the single diastereomeric compound **6** as the substrate for the Achmatowicz rearrangement, which occurred smoothly with *m*-chloroperoxybenzoic acid (*m*CPBA) to provide the spiro-dihydropyranone acetal framework.[15] Protection of the labile acetal as benzyl ether delivered **7** with a 1 : 1 diastereomeric ratio at the acetal carbon. The excellent scalability of the Achmatowicz rearrangement allowed us to prepare **7** on a 30-gram scale.

With a reliable supply of spiro-framework **7** in hand, we set out to functionalize the dihydropyranone into the lactone corresponding to aogacillins. Installation of the methyl group at C3 was performed with a methyl Grignard reagent followed by $PhSeCl/H_2O_2$ (ref. 16) to afford compound **8** in 48% yield. $CeCl_3$ mediated nucleophilic 1,2-addition[17] of MeLi to **8** delivered inseparable products with poor yield. Improvement of the yield was attempted without success due to the extraordinary steric hindrance from the adjacent quaternary carbon (similar to the neopentyl effect). After TMS protection of the tertiary alcohol, the diastereoisomers **9a** and **9b** could be separated by flash column chromatography on silica gel and used individually in the subsequent reactions. The Upjohn dihydroxylation was found to proceed slowly with low conversion even after 5 days. Fortunately, ruthenium-catalyzed *syn*-dihydroxylation[18] could afford the desired diols **10a** and **10b** as well as over oxidized hydroxyketones **11a** and **11b** in moderate yields. The diols **10a**/**10b** could also be oxidized to hydroxyketones using IBX. The structures of **10a** (CCDC 2464462) and **11b** (CCDC 2464461) were further confirmed by X-ray crystallographic analysis. It is interesting to note that the methyl and ethyl groups on the cyclohexane moiety of **11b** are in the equatorial positions based on the X-ray data, while the hydroxyketone **10a** places the methyl and ethyl groups in the unfavorable axial positions. With **11a** and **11b** in hand, we tried to accomplish the total synthesis by transforming the benzyl acetal to lactone as well as dehydrating the C-5 tertiary alcohol to a terminal alkene. However, we encountered unexpected difficulty in dehydration under various conditions and suspected that the adjacent carbonyl might be responsible for the failure of dehydration. We also tried to perform the dihydroxylation from **8** and protection as acetonides **13a**/**13b**. Then olefination was tested using the Wittig reagent, Peterson conditions ($TMSCH_2MgCl$),[19] Tebbe reagent,[20] and Petasis reagent,[21] but unfortunately, none of them could deliver the desired olefin. Methyl addition and dehydration did not work either due to decomposition. This failure forced us to re-design a new synthetic strategy that was not based on the Achmatowicz rearrangement.

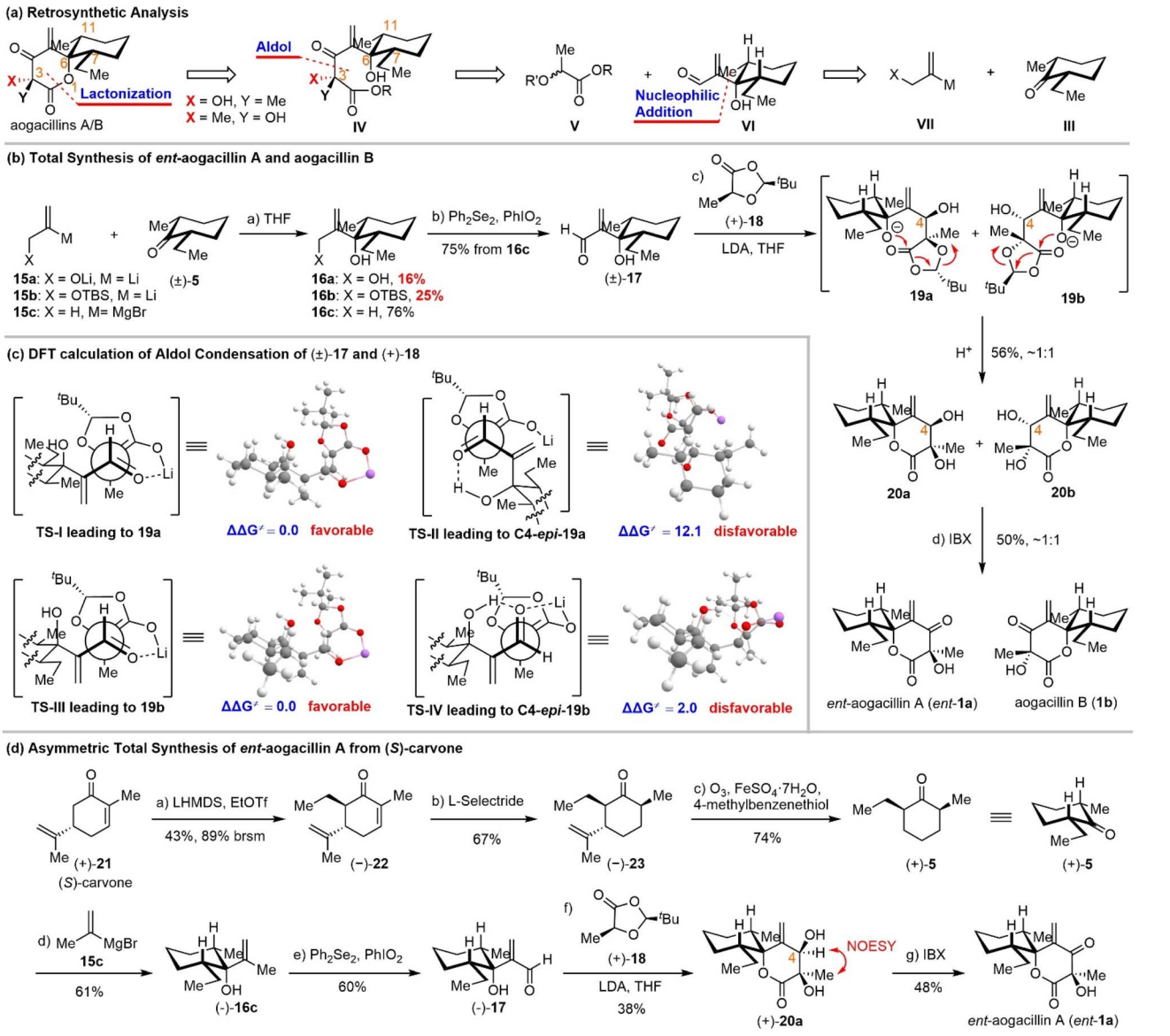
We recognized that there was one major obstacle in the Achmatowicz rearrangement-based strategy: unsuccessful olefination of the C5 carbonyl due to the extraordinary steric hindrance and electronic effects of the neighboring functional



Scheme 2 Synthetic efforts towards aogacillins A and B based on the Achmatowicz rearrangement strategy.

groups. In order to avoid this problem, we proposed to install this terminal alkene at an early stage through vinyl metallic reagent addition to *cis*-2-ethyl-6-methyl-cyclohexanone (Scheme 3a, **III** + **VII** →**VI**). The δ-lactone could be constructed by aldol condensation of lactic acid derivative **V** and β-hydroxyl-α-methylene-aldehyde **VI** followed by lactonization.

Initially, 2-bromoallyl alcohol and TBS protected 2-bromoallyl alcohol were employed for lithium–halogen exchange to generate *in situ* the requisite alkenyl lithium reagents **15a**/**15b**, which were added to *cis*-2-ethyl-6-methyl-cyclohexanone **5** (Scheme 3b). Unfortunately, both reactions gave **16a**/**16b** in poor yields (16% and 25%, respectively). We suspected that the lithium alkoxide might aggregate in the solution and disfavor the nucleophilic addition to the bulky enolizable ketone **5**. If *tert*-butyldimethylsilyl (TBS) ether **15b** was used as the protecting group, the propargyl addition product became the major byproduct. To improve this nucleophilic addition, we chose the isopropenyl Grignard reagent **15c** for the addition to *cis*-2-ethyl-6-methyl-cyclohexanone **5** and performed an allylic oxidation with $Ph_2Se_2/PhIO_2$ (ref. 22) to obtain the aldehyde **17** in 76% yield. It is noteworthy that the allylic oxidation with SeO_2 under conventional conditions[23] proceeded in only 15% yield. Next, aldol condensation of racemic aldehyde **17** and Seebach–Fráter chiral 1,3-dioxolan-4-one **18** (prepared through condensation of (*S*)-lactic acid and 2,2-dimethylpropanal)[24] afforded an inseparable 1 : 1 mixture of lactones **20a** and **20b**, which might be derived from an intramolecular lactonization (**19a**/**b** → **20a**/**b**). The subsequent IBX oxidation of **20a**/**20b** furnished a mixture of aogacillin B and the enantiomer of aogacillin A, which were finally separated by reversed-phase preparative HPLC. The spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) and specific rotation of our synthetic materials were consistent with those



Scheme 3 Total syntheses of aogacillin B and *ent*-aogacillin A.

reported for the natural products (Tables S1 and S2). It should be noted, however, that the HPLC separation was very inefficient. Only 5.8 mg of pure *ent*-aogacillin A and 4 mg of pure aogacillin B could be obtained from 40 mg of their mixture.

The accomplishment of the first total synthesis of aogacillins warranted some comments. First, the strategic use of Seebach–Fráter chiral 1,3-dioxolan-4-one **18** for the aldol reaction with racemic aldehyde was expected to deliver enantiomerically pure aogacillins if the diastereomeric products **20a**/**20b** could be separated through column chromatography. This idea was achieved finally by chiral HPLC and thus our total synthesis is asymmetric. Second, β-hydroxyl-α-methylene aldehyde (*i.e.*, **17**) was employed for the first time in the aldol reaction with 1,3-dioxolanones and the concomitant lactonization, which offers a new venue for the synthesis of functionalized δ-lactones. Third, stereochemical outcomes from the sequential aldol reaction/lactonization are intriguing because only two diastereomers were isolated among eight possible stereoisomers (Scheme 3c). This suggested that the aldol reaction of **17a**/**b** with **18** was highly diastereoselective. Density functional theory (DFT) calculations were performed to predict the configurations of the newly formed C-4 hydroxyl groups. DFT calculations showed that the energy barrier of transition state TS-II leading to C4-*epi*-**19a** is higher than that of TS-I leading to **19a**; meanwhile, the Gibbs free energy of C4-*epi*-**19a** is also higher than that of **19a**. This indicates that **19a** is favored both kinetically and thermodynamically (see the SI). The energy barrier of transition state TS-IV leading to C4-*epi*-**19b** is higher than that of TS-III leading to **19b**; however, the Gibbs free energy of C4-*epi*-**19b** is lower than that of **19b**. (see the SI) This indicates that **19b** is favored kinetically and C4-*epi*-**19b** is favored thermodynamically. As we conducted the reaction at −78 °C, the kinetically controlled product **19b** should be the major product. Besides, it should be noted that this calculated stereochemical outcome is different from those reported by Seebach[24] and Battaglia,[25] but is consistent with those predicted by Zimmerman–Traxler models, although the β-hydroxyl aldehyde would form intramolecular hydrogen bonds.

Since a mixture of aogacillin B and *ent*-aogacillin A was obtained due to the use of racemic *cis*-2-ethyl-6-methyl-cyclohexanone (±)-**5** and HPLC separation was required, we proposed to synthesize optically active (or pure) *cis*-2-ethyl-6-methyl-cyclohexanone **5** and expected to achieve the asymmetric synthesis of either aogacillin A or aogacillin B. To this end, we employed (*S*)-carvone as the chiral non-racemic starting material for the preparation of (+)-**5** (Scheme 3d). α-Alkylation of (*S*)-carvone with ethyl triflate afforded the *trans* ethyl addition product (−)-**22** with excellent diastereoselectivity. Although the conversion was low even using 5 equivalents of ethyl triflate, (*S*)-carvone could be recycled. The conjugate reduction with L-selectride could give (−)-**23** in 67% yield with high diastereoselctivity. Under Kwon's hydrodealkenylation conditions,[26] enantio-pure *cis*-2-ethyl-6-methyl-cyclohexanone (+)-**5** could be prepared smoothly in 74% yield. Following the Grignard addition and allylic oxidation procedures as for the racemic substrate, enantiopure **17** was synthesized. The next aldol condensation with Seebach–Fráter chiral 1,3-dioxolan-4-one **18** afforded enantiopure lactone **20a**. The absolute configuration of the C-4 hydroxyl group was confirmed by the NOESY spectrum. This was consistent with the DFT calculation results. Final oxidation with IBX accomplished the enantioselective synthesis of *ent*-aogacillin A.

Conclusions

In summary, we have explored two synthetic strategies for the total synthesis of the bioactive natural products aogacillins and achieved the first total synthesis of *ent*-aogacillin A and aogacillin B in 7 steps. The first strategy hinges on Achmatowicz rearrangement but fails to furnish aogacillins due to the unsuccessful olefination of C5 ketone which is sterically hindered and enolizable. To overcome this challenge, we redesigned our synthetic strategy which features the installation of the terminal alkene at an early stage and the construction of the spirocyclic δ-lactone scaffold through a newly developed diastereoselective one-pot aldol reaction and concomitant lactonization, which, as a new method, might be applicable to the synthesis of other fully functionalized δ-lactones and δ-lactone-containing natural products.

Author contributions

H. G., Z. L., R. S., J. R., X. C., B. M., W. Q., Z. Y. and W. Z. performed the synthetic experiments. H. G. and Z. L. contributed equally to this work. X. Z. conducted the HPLC isolation. Z. L. performed the DFT calculations. W. Z., R. T. and X. L. supervised and provided guidance to the project. W. Z. drafted the manuscript and SI. R. T. revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2464461 (**11b**) and 2464462 (**10a**) contain the supplementary crystallographic data for this paper.[27a,b]

Experimental procedures and characterization data are available within this article and its supplementary information (SI). Data are also available from the corresponding author on request. Supplementary information is available. See DOI: https://doi.org/10.1039/d5sc04554a.

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