Total Synthesis of Penicyclone A Using a Double Grignard Reaction
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ABSTRACT: We describe the first total synthesis of penicyclone A, a novel deep-sea fungus-derived polyketide, and a reevaluation of its antimicrobial activity. The synthesis of this unique spirolactone was achieved in 10 steps starting from a known D-ribose derivative. The key steps include a double Grignard reaction for the diastereoselective construction of the chiral tertiary alcohol intermediate, tandem oxidation/cyclization, and photooxygenation, followed by an oxidative rearrangement to introduce the enone functionality.

INTRODUCTION

Penicyclone A is a deep-sea derived natural product containing a spiro[5,5]lactone.¹ This structural motif is rare with only a few natural products reported to date.² As such, it presents a considerable synthetic challenge owing to the limited scope of methods applicable for the construction of such a moiety. Our motivation for the synthesis of penicyclone A, aside from its exotic structure, was its reported antibacterial activity. Bacterial resistance to current antibiotics in medicinal use presents a significant challenge in health care.³ One approach to resolving this challenge is the synthetic modification of existing scaffolds to bypass antimicrobial resistance (AMR). However, derivatives of a compound to which bacteria is already resistant pose a high risk of bacterial adaptation. To alleviate this risk, it is beneficial to explore the antimicrobial activity of completely new scaffolds.⁴ In 2015, Li and coworkers reported the isolation of penicyclones A–E, a family of polyketide secondary metabolites that were harvested from the fungus Penicillium sp. F23-2 when the fungal strain was cultured on a rice-based solid medium.¹ This fungal strain was known for producing cytotoxic nonribosomal peptide synthetases (NRPS) alkaloids and terpenoids in a potato-based medium under static conditions,⁵ as well as nitrogen-containing polyketides (sorbicillinoids) in agitated peptone yeast glucose broth (PYG) medium.⁶ The one-strain-many-compounds (OSMAC) approach along with altering the cultivation conditions resulted in the isolation of these new secondary metabolites. After isolation, the compounds were not only thoroughly characterized, but their minimum inhibitory concentration (MIC) values were also measured to have impressive results for Staphylococcus aureus, especially in the case of penicyclone A (0.3 μg/mL). In contrast with NRPS alkaloids, these penicyclone compounds showed no cytotoxic activity toward HeLa, BEL-7402, KEK-293, HCT-116, and A549 cell lines (IC₅₀ > 50 μM).

Penicyclone A is a derivative of ambuic acid, which, along with the structurally related jesterone as well as the dimeric torreyanic acid, has been a synthetic target for some time (Figure 1).⁷ In contrast to these derivatives, penicyclone A features a unique six-membered spirolactone adjacent to a highly substituted cyclohexanone core.

Figure 1. Structure of penicyclone A, ambuic acid, jesterone, and torreyanic acid.

Received: September 13, 2022
Published: November 16, 2022
functional groups and chiral centers in a relatively small molecule presents a considerable synthetic challenge. Herein, we report the first total synthesis of penicyclone A, which was accomplished in 10 steps starting from a known D-ribose derivative.

■ RESULTS AND DISCUSSION

Our retrosynthetic analysis (Scheme 1) eventually led to D-ribose, which could be used as a cheap and optically pure source of the cis-diol moiety. The challenge with using a carbohydrate precursor was turning the interrupted carbon chain into the cyclohexane ring of penicyclone A. We envisioned that a double Grignard reaction of 5 (obtained from D-ribose in four steps with 67% overall yield) with allylmagnesium bromide and 6 would enable a diastereoselective construction of the tertiary alcohol 7a with substituents that would later become parts of both rings. It is generally regarded that the addition of Grignard reagents to esters or lactones forms tertiary alcohols with two identical substituents owing to the higher reactivity of the ketone intermediate. However, there are several reports on specific substrates that demonstrate the possibility of a mono addition. We hypothesized that a sequential addition (1 eq of the first Grignard reagent followed by the addition of the second) might be possible when using protected sugar-derived lactones as starting materials. This transformation could lead to the diastereoselective formation of tertiary alcohols due to chelation control during the second nucleophilic attack (Scheme 2).

We thus reacted 5 at low temperature with allylmagnesium bromide followed by the addition of TBS-protected 4-hydroxybutylmagnesium bromide 6. To our delight, the assumption was correct, and 7a was obtained as a single diastereomer as determined by 1H NMR. Using this approach, 8 was obtained on the gram scale after TBAF-mediated silyl deprotection in an isolated yield of 57% over two steps from 5. The major side product 7b could be readily separated by column chromatography. Both the relative and absolute configuration of the TBS-protected tertiary alcohol 7a were confirmed by X-ray diffraction. This is, to the best of our knowledge, the first example of a diastereoccontrolled synthesis of tertiary alcohols from lactones using the Grignard reaction.

With 8 in hand, our focus was set on closing the lactone ring (Scheme 3). To that end, we first attempted reacting 8 with silver carbonate on Celite. This method is used to oxidize primary alcohols to aldehydes, which form intramolecular semiacetals (cyclization with tertiary OH group) that are quickly oxidized to lactones. After several runs, we observed significant batch-to-batch variations in reaction time and yield. We then turned to the TEMPO/PIDA catalytic system. These conditions efficiently closed the lactone ring but oxidized the secondary alcohol slowly and only partially. Thus, after complete conversion to the lactone was confirmed by TLC, Dess–Martin periodinane (DMP) was added, resulting in a one-pot formation of 9 in 97% yield on gram scale.

The methylenation of the newly installed ketone was explored next. Surprisingly, the compound proved inert to classical olefination reagents such as phosphorus ylide and...
titanium-based reagents. This result was rationalized to be due to steric hindrance from two neighboring rings, so we tried using smaller reagents. After extensive experimentation, we found that the diene \( \text{11} \) could be obtained using \( \text{10} \) in a modified Julia−Kociensky reaction. Subsequent ring closing metathesis proceeded smoothly to produce the advanced spirolactone intermediate \( \text{12} \) in an excellent 95% yield on gram scale. This intermediate closely resembles penicyclone A, requiring only the installation of the methyl group at C-9 and the carbonyl functionality at C-1. Our initial plan was to use an enantiomerically pure methylated derivative of the Grignard reagent \( \text{6} \), introducing the C-9 methyl at an early stage (see the SI). Unfortunately, the Julia−Kociensky reaction with C-9-methylated \( \text{9} \) proceeded in low yield and resulted in complete epimerization regardless of the conditions used. This forced us to introduce the methyl group at a late stage using MeI and NaHMDS on compound \( \text{12} \), yielding \( \text{13} \) and its C-9 epimer \( \text{14} \) in a 1:1.5 d.r. and 80% combined yield. After chromatographic separation of \( \text{13} \), compound \( \text{14} \) could be epimerized to a 1:1.25 mixture of diastereomers in 92% yield using a catalytic amount of KOtBu in THF to afford additional amounts of \( \text{13} \).

The final challenge was the allylic oxidation at C-1. To facilitate our pursuit of the right oxidation conditions, we used \( \text{12} \) as a model compound since it was easier to obtain. Our initial screening focused on methods that could provide the enone directly. Oxidation of \( \text{12} \) using the \( \text{Rh}_2(\text{cap})_2(\text{CH}_3\text{CN})_2/\text{TBHP} \) system developed by Doyle and coworkers yielded \( \text{18} \) (Scheme 4) as the major product along with significant substrate decomposition. On the other hand, using \( \text{SeO}_2/\text{KH}_2\text{PO}_4 \) in nitromethane, \( \text{NHS/Na}_2\text{Cr}_2\text{O}_7 \) in acetone, \( \text{Cu/TPB} \) in acetone, \( \text{Pd/C/TBHP} \) in DCM, \( \text{19} \) was obtained as the major product. This indicated that hydrogen abstraction at C-4 is the dominant oxidation pathway when radical oxidants were used. Next, we explored \( \text{SeO}_2 \)-based allylic oxidation in toluene with \( \text{KH}_2\text{PO}_4 \) under reflux, which yielded a mixture of alcohol and aldehyde \( \text{20} \). The reaction of \( \text{12} \) with stoichiometric \( \text{SeO}_2 \) in dioxane with phosphate buffer resulted in ester hydrolysis yielding \( \text{21} \), while the reaction in unbuffered dioxane led to complete...
decomposition of the starting material. This was also the result when the reaction was performed using catalytic SeO₂ in DCM with TBHP as the stoichiometric oxidant.

Surprisingly, upon exploration of chromium-based oxidants, the substrate proved to be inert toward PCC oxidation under various conditions. Oxidation using the CrO₃/3,5-DMP system yielded 22, indicating once again the higher reactivity at C-4 in contrast to C-1. In order to activate the C-1 position, we also explored the allylic bromination of 12 using NBS in CCl₄, which resulted in the formation of 23, albeit in a moderate yield. Unfortunately, further oxidation to the enone using PNO and silver salts resulted in elimination instead.

The photooxygenation of 12 was explored next, but the reaction did not occur regardless of the photosensitizer or solvent used. This lack of reactivity was rationalized by an unfavorable H—CH—C=C dihedral angle in the singlet oxygen perepoxide transition state. We hypothesized that the removal of the cis-diol protecting group would enable a hydroxyl group-directed singlet oxygen ene reaction on the previously sterically inaccessible face of the double bond. To this end, we removed the protecting group using TFA in DCM and obtained the unprotected diol 24. To our delight, the oxidation of the diol 24 proceeded smoothly and delivered the peroxide 25 as a single diastereomer (Scheme 5). Our first plan relied on a Schenk rearrangement of 25 that would yield 26, which in turn could be dehydrated to the enone. However, the rearrangement did not occur under a variety of tested conditions, likely due to strong intramolecular hydrogen bonding.

The other option was to reduce the peroxide to the tertiary alcohol and use an oxidative rearrangement to introduce the enone functionality. This would require the reprotection of the cis-diol, which could not be performed regioselectively due to the presence of the tertiary alcohol. Thus, a protecting group swap was conducted before the photooxygenation, inducing the conformational change that was required for the reaction to proceed and, on the other hand, enable further oxidative rearrangement (Scheme 6). Upon the reaction with singlet oxygen, 27 yielded a mixture of 28 and 29 due to loss of hydrogen bonding, which directed the reaction in the case of compound 24. Finally, after reductive workup, 30 was successfully oxidized to the enone 31 using a PCC/PIDA system. It should be noted that the Schenk rearrangement of 28 was examined as well, but it produced only small amounts of the rearranged product at high temperatures, accompanied by substantial substrate decomposition.

With an end game strategy in hand, this method was used on the C-9 methylated substrate 15 yielding alcohol 16, which was oxidatively rearranged to the TMS-protected enone 17. Compound 17 was characterized by SCXRD, and the presence of silicon atoms in TMS enabled assignment of its absolute configuration. Removal of both TMS groups using TFA in methanol yielded the final product, penicyclone A (1).

The biological activity of penicyclone A was reevaluated on the synthetic sample. The antimicrobial activity was tested against S. aureus (ATCC 29213), Enterococcus faecalis (ATCC 29212), Moraxella catarrhalis (ATCC 23246), and Escherichia coli (ECM 1556) in two separate laboratories, and the compound showed no antimicrobial activity (MIC > 32 μg/mL) on all tested strains (see the SI). The previously reported results for isolated penicyclone A could be due to a highly potent impurity present in the isolated sample.
CONCLUSIONS

In summary, we performed the first asymmetric total synthesis of penicyclone A, which was accomplished in 10 steps starting from a known ribose derivative. We chose the target molecule as it exhibited significant antimicrobial activity toward S. aureus after it was recently isolated from a deep-sea fungus Penicillium sp. F23-2. The key synthesis step was the construction of a tertiary alcohol using a diastereoselective double Grignard reaction on a modified sugar. We recognize that this methodology might offer a simple approach to various constructions of a tertiary alcohol using a diastereoselective double Grignard reaction on a modified sugar. We recognize that this methodology might offer a simple approach to various.

Another significant challenge was the late-stage introduction of the enone, which was accomplished by using a photooxygenation/oxidative rearrangement sequence. Upon reevaluation of the reported biological activity, the compound showed no antimicrobial activity against the tested bacterial strains.

EXPERIMENTAL SECTION

All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Volatile solvents were removed under reduced pressure rotary evaporation at 35 °C. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm Merck silica plates (60F254), using UV light as the visualizing agent and KBrO3 and heat as the developing agent. Dichloromethane (DCM) and methanol (MeOH) were dried using activated 3 Å molecular sieves. Tetrahydrofuran (THF), diethyl ether (Et2O), and toluene were distilled over sodium before use. Methyl-1-(bromobutoxy)-tert-butyl)-5-(methylsulfonyl)-1H-tetrazole (10),12,13 Dess–Martin periodinane (DMP),23 S-deoxy-2,3-isopropylidene-n-ribonolactone (5),24 and 4-bromobutoxy)(1 tert-butyl)dimethylsilane (32)25 were previously prepared ac-cording to literature procedures. All other reagents were acquired from commercial sources and used without further purification. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material unless otherwise stated. Silica gel chromatography was performed using Merck silica gel (60, particle size 0.040–0.063 mm). NMR spectra were recorded on Bruker Ascend 400 and Bruker Ascend 600 instruments at 298 K and were calibrated using residual undeuterated solvent as an internal reference (CHCl3).

To a solution of lactone 5 (4.00 g, 23.2 mmol, 1.0 equiv) in Et2O (150 mL) and THF (23 mL) at −78 °C, a solution of allyl magnesium bromide (23.2 mL, 1.0 M in Et2O, 1.0 equiv) was added dropwise over 40 min. The reaction was stirred for 35 min at −78 °C, and then, a freshly prepared solution of 6 (2.0 equiv) was added over 10 min. The resulting suspension was warmed to room temperature over 45 min, stirred at room temperature for 30 min, and then quenched by the addition of sat. NH4Cl (80 mL). After stirring for 10 min, H2O (10 mL) was added, and the layers were separated. The aqueous layer was extracted twice with Et2O (50 mL), and the combined organic extracts were washed with brine (30 mL), dried with Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography (15% EtOAc/Hex to 30% EtOAc/Hex) to give 7a as a single diastereomer containing 7b (ca. 15 mol %, according to 1H NMR), which was taken into the next step according to further purification (6.525 g). An analytically pure sample of 7a was obtained as a white solid by a second chromatographic purification (50% EtOAc / DCM).

Synthesis of Compound 7a.

To a solution of 7a (6.525 g, 16 mmol) in DCM (42 mL) was added TBAF (42 mL, 1.0 M in THF), and the resulting orange solution was stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by column chromatography (EtOAc) to give 8 (3.87 g, 57% over two steps) as a viscous, colorless oil.

Synthesis of Compound 8.

To a solution of 7a (6.525 g, 16 mmol) in DCM (42 mL) was added TBAF (42 mL, 1.0 M in THF), and the resulting orange solution was stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by column chromatography (EtOAc) to give 8 (3.87 g, 57% over two steps) as a viscous, colorless oil.

CONCLUSIONS

In summary, we performed the first asymmetric total synthesis of penicyclone A, which was accomplished in 10 steps starting from a known ribose derivative. We chose the target molecule as it exhibited significant antimicrobial activity toward S. aureus after it was recently isolated from a deep-sea fungus Penicillium sp. F23-2. The key synthesis step was the construction of a tertiary alcohol using a diastereoselective double Grignard reaction on a modified sugar. We recognize that this methodology might offer a simple approach to various complex tertiary alcohols, and we are currently investigating the reaction mechanism and its scope. Another significant challenge was the late-stage introduction of the enone, which was accomplished by using a photooxygenation/oxidative rearrangement sequence. Upon reevaluation of the reported biological activity, the compound showed no antimicrobial activity against the tested bacterial strains.

EXPERIMENTAL SECTION

All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Volatile solvents were removed under reduced pressure rotary evaporation at 35 °C. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm Merck silica plates (60F254), using UV light as the visualizing agent and KBrO3 and heat as the developing agent. Dichloromethane (DCM) and methanol (MeOH) were dried using activated 3 Å molecular sieves. Tetrahydrofuran (THF), diethyl ether (Et2O), and toluene were distilled over sodium before use. Methyl-1-(bromobutoxy)-tert-butyl)-5-(methylsulfonyl)-1H-tetrazole (10),12,13 Dess–Martin periodinane (DMP),23 S-deoxy-2,3-isopropylidene-n-ribonolactone (5),24 and 4-bromobutoxy)(1 tert-butyl)dimethylsilane (32)25 were previously prepared ac-cording to literature procedures. All other reagents were acquired from commercial sources and used without further purification. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material unless otherwise stated. Silica gel chromatography was performed using Merck silica gel (60, particle size 0.040–0.063 mm). NMR spectra were recorded on Bruker Ascend 400 and Bruker Ascend 600 instruments at 298 K and were calibrated using residual undeuterated solvent as an internal reference (CHCl3); 1H NMR δ = 7.26 ppm, 13C NMR δ = 77.16 ppm. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Q, extractive ESI Orbitrap mass spectrometer. Circular dichroism (CD) spectra were recorded on a JASCO J815 spectrophotometer in methanol (spectroscopic grade) using appro-
(bs, 1H), 2.49 (d, J = 7.5 Hz, 2H), 2.11 (bs, 1H), 1.84–1.76 (m, 1H), 1.67–1.41 (m, 5H), 1.43 (s, 3H), 1.32 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H);

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$): δ/ppm 133.3, 119.4, 107.1, 81.8, 80.8, 74.4, 65.4, 62.5, 41.3, 34.8, 32.9, 28.3, 25.9, 19.9, 18.9.

**Synthesis of Compound 9.**

To a solution of 8 (150 mg, 0.52 mmol, 1 equiv) in DCM (5 mL) open to air was added PIDA (840 mg, 2.61 mmol, 5 equiv) and TEMPO (16.5 mg, 0.106 mmol, 20 mol %). The mixture was stirred at room temperature for 90 min, DMP (310 mg, 0.73 mmol, 1.4 equiv) was added, and the mixture was stirred for an additional 2 h and 10 min. The reaction was quenched by dilution with Et$_2$O (10 mL), the resulting suspension was concentrated, and the crude residue was purified by column chromatography (30% EtOAc/Hex), giving 9 (143 mg, 97%) as a pale yellow oil that crystallized overnight to a white solid.

**Compound 9:**

RF = 0.50 (30% EtOAc/Hex, KMN$_5$O$_4$); [α]$_D^{23}$ = −23.0 (c 0.89, CHCl$_3$);

IR (ATR) $\nu_{\max }$(cm$^{-1}$): 3086, 2978, 1731, 1703, 1645;

HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcd for C$_{16}$H$_{18}$O$_5$ 283.1545; found 283.1545;

$^1$H NMR (600 MHz, CDCl$_3$): δ/ppm 5.65 (m, 1H), 5.24 (dd, J = 7.9 Hz, 1H), 4.35 (d, J = 7.9 Hz, 1H), 2.88–2.82 (m, 1H), 2.53–2.51 (m, 3H), 2.27 (s, 3H), 2.07–2.00 (m, 1H), 1.95–1.74 (m, 3H), 1.68 (s, 3H), 1.38 (s, 3H);

**Synthesis of Compound 11.**

To a solution of 9 (2.63 g, 9.32 mmol, 1 equiv) and 10 (2.81 g, 18.65 mmol, 2 equiv) in THF (130 mL) at −78 °C was added NaHMDS (12.14 mL, 12.14 mmol, 1.0 M in THF, 1.3 equiv) at once, and the solution was left to slowly warm to room temperature overnight (16 h). The reaction was quenched by saturated aqueous NH$_4$Cl (40 mL), the layers were separated, and the aqueous layer was extracted with Et$_2$O (2 × 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by column chromatography (DCM to 20% EtOAc/DCM), giving 11 (1.40 g, 54%) as a white, crystalline solid.

**Compound 11:**

RF = 0.63 (15% EtOAc/DCM, KMN$_5$O$_4$); [α]$_D^{12}$ = −24.2 (c 1.1, CHCl$_3$);

IR (ATR) $\nu_{\max }$(cm$^{-1}$): 3079, 2982, 2963, 2913, 1728, 1642, 1035;

HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for C$_{10}$H$_{14}$O$_3$Na 303.1572; found 303.1569;

$^1$H NMR (400 MHz, CDCl$_3$): δ/ppm 5.79 (m, 1H), 5.19–5.13 (m, 2H), 5.08 (m, 1H), 5.02 (m, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.22 (d, J = 6.8 Hz, 1H), 2.60 (dq, J = 15.4 Hz, 7.4 Hz, 2H), 2.50–2.43 (m, 1H), 2.40–2.31 (m, 1H), 1.96–1.73 (m, 7H), 1.59 (s, 3H), 1.37 (s, 3H);

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$): δ/ppm 170.5, 143.2, 132.4, 119.9, 114.7, 108.0, 85.0, 80.7, 80.3, 40.5, 30.0, 26.5, 25.5, 24.9, 20.9, 16.6.

**Synthesis of Compound 12.**

To a solution of 11 (1.40 g, 5 mmol, 1 equiv) in toluene (125 mL) was added Grubbs-Hoveyda II (100 mg, 0.16 mmol, 3 mol %) catalyst, and the mixture was stirred at room temperature and 200 mBar. After 3 h, the mixture was concentrated, and the crude residue was purified by column chromatography (60% EtOAc/Hex), giving 12 (1.20 g, 95%) as an off-white solid due to traces of ruthenium. This compound could be further purified by an additional column chromatography (60% EtOAc/Hex), but this impurity did not affect the next steps and got removed during the next purification.

**Compound 12:**

RF = 0.46 (60% EtOAc/Hex, KMN$_5$O$_4$); [α]$_D^{23}$ = −73.6 (c 1.0, CHCl$_3$);

IR (ATR) $\nu_{\max }$(cm$^{-1}$): 2964, 2913, 1731, 1044;

HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for C$_{16}$H$_{16}$O$_4$Na 275.1259; found 275.1257;

$^1$H NMR (600 MHz, CDCl$_3$): δ/ppm 5.33 (m, 1H), 4.53 (d, J = 5.5 Hz, 1H), 4.15 (dd, J = 5.5 Hz, 1.0 Hz, 1H), 2.59–2.48 (m, 2H), 2.40–2.35 (m, 1H), 2.27–2.22 (m, 1H), 2.08–2.03 (m, 1H), 2.00–1.93 (m, 1H), 1.91–1.84 (m, 1H), 1.83–1.79 (m, 1H), 1.78 (m, 3H), 1.39 (s, 3H), 1.36 (s, 3H);

$^{13}$C($^1$H) NMR (151 MHz, CDCl$_3$): δ/ppm 170.6, 132.9, 118.8, 109.8, 83.2, 76.6, 76.3, 33.5, 30.0, 29.8, 27.5, 26.9, 19.5, 16.0.

**Synthesis of Compound 13.**

To a solution of 12 (200 mg, 0.793 mmol, 1 equiv) in THF (6.5 mL) at −78 °C was added NaHMDS (800 μL, 1 M in THF, 1.01 equiv) dropwise over 5 min. The mixture was stirred at −78 °C for 30 min, and methyl iodide (100 μL, 1.6 mmol, 2 equiv) was added dropwise. The mixture was warmed to −50 °C over 2 h and then warmed to room temperature over 30 min. The mixture was concentrated and purified by column chromatography (30% EtOAc/Hex) to give 13 and 14 (170.4 mg, 80%) as a 1:1.5 mixture of diastereomers. The diastereomers could be separated by column chromatography (10% EtOAc/Hex), and both were obtained as white crystalline solids.

**Compound 13:**

RF = 0.33 (30% EtOAc/Hex, KMN$_5$O$_4$); [α]$_D^{23}$ = −85.3 (c 0.40, CHCl$_3$).
IR (ATR) $\nu_{\text{max}}$ (cm$^{-1}$): 2987, 2918, 1723, 1028;
HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ calcld for C$_{13}$H$_{12}$O$_4$ 267.1591; found 267.1595;

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$/ppm 5.35–5.33 (m, 1H), 4.54 (d, $J = 5.5$ Hz, 1H), 4.12 (dd, $J = 5.7$ Hz, 0.7 Hz, 1H), 2.56–2.50 (m, 1H), 2.36–2.24 (m, 2H), 2.05–1.96 (m, 3H), 1.78 (m, 3H), 1.68–1.61 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.30 (d, $J = 7.1$ Hz, 3H);

$^{13}$C(CH$_3$) NMR (151 MHz, CDCl$_3$): $\delta$/ppm 174.1, 133.0, 119.1, 109.7, 83.4, 78.2, 76.4, 35.7, 33.3, 29.8, 27.4, 26.8, 24.8, 19.6, 17.8.

**Synthesis of Compound 16.**

To a solution of 15 (49 mg, 132 $\mu$mol, 1 equiv) in CDCl$_3$ (5 mL) under an atmosphere of O$_2$ was added TPP (2 mg, 3.25 $\mu$mol, 2.5 mol %), and the solution was irradiated with a 250 W tungsten halogen lamp projector at room temperature. After 14 h, Ph$_2$P (45 mg, 172 $\mu$mol, 1.3 equiv) was added, and the mixture was stirred for an additional 5 min. The mixture was concentrated, and the crude residue was purified by column chromatography (25% EtOAc/Hex), giving 16 (12.38 mg, 32 $\mu$mol, 24%, 59% BRSM) as a colorless oil, 33 (4.72 mg, 9%, 23% BRSM) as a colorless oil, and recovered starting material 15 (29.0 mg, 78 $\mu$mol, 59%).

**Synthesis of Compound 17.**

To a solution of 16 (15.0 mg, 38.8 $\mu$mol, 1 equiv) in DCM (300 $\mu$L) under an atmosphere of O$_2$ was added PDA (7.1 mg, 114.9 $\mu$mol, 3 equiv) and PCC (1.0 mg, 4.7 $\mu$mol, 14 mol%). The mixture was stirred at room temperature for 18 h and then directly purified by column chromatography (25% EtOAc/Hex), giving 17 (4.33 mg, 11.3 $\mu$mol, 29%, 83% BRSM) as a white, crystalline material and recovered starting material 16 (9.72 mg, 65%).

**Synthesis of Compound 14.**

To a solution of 14 (104 mg, 0.39 mmol, 1 equiv) in THF (1.9 mL) was added KOIBu (1.9 mL, 0.01 M solution in THF, 5 mol %), and the mixture was stirred at room temperature for 10 min. The reaction was quenched with ammonium chloride (15 mg) and stirred for 5 min. The mixture was filtered, and the solids were washed twice with Et$_2$O (3 mL) and concentrated. The crude residue was purified by column chromatography (30% EtOAc/Hex) to give 13 (95.4 mg, 92%) as a 1:1.25 mixture of diastereomers. The diastereomers could be separated by column chromatography (10% EtOAc/Hex).

**Synthesis of Compound 15.**

To a solution of 13 (51 mg, 0.192 mmol, 1 equiv) in DCM (1 mL) open to air was added TFA (1 mL) and H$_2$O (25 $\mu$L). The mixture was stirred at room temperature for 1 h and 30 min. The mixture was concentrated, the crude residue was dissolved in MeNO$_2$ (1 mL), and HMDS (100 $\mu$L, 0.477 mmol, 2.48 equiv) was added. The mixture was stirred at room temperature for 5 min and concentrated, and the crude residue was purified by column chromatography (Hex to 10% EtOAc/Hex), giving 15 (49 mg, 0.132 mmol, 69%, 80% BRSM) as a colorless oil and recovered starting material 13 (7.3 mg, 0.0274 mmol, 14%).

**Compound 15.**

IR (ATR) $\nu_{\text{max}}$ (cm$^{-1}$): 2956, 2878, 1731, 834;
HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcld for C$_{13}$H$_{14}$O$_4$Na 393.1893; found 393.1893;
To a solution of 10 (10.36 mg, 26.94 μmol, 1 equiv) in MeOH (1 mL) was added TFA (10 μL), and the mixture was stirred at room temperature open to air for 20 min. The mixture was concentrated, and the crude residue was purified by column chromatography (EtOAc), giving 1 (5.25 mg, 21.83 μmol, 81%) as a colorless crystalline material.

**Synthesis of Compound 1.**

[Diagram showing the synthesis process]

**REFERENCES**

1. Guo, W.; Zhang, Z.; Zhu, T.; Gu, Q.; Li, D.; Penicyclones, A. E. Antibacterial Polyketides from the Deep-Sea-Derived Fungus Penicillium Sp. F23-2. J. Nat. Prod. 2015, 78, 2699–2703.
2. (a) Pratavull, A. Spiroactones: Recent Advances in Natural Products, Bioactive Compounds and Synthetic Strategies. Curr. Med. Chem. 2018, 25, 917–962. (b) Takata, K.; Ikawaishi, M.; Yamamoto, T.; Shirahata, T.; Nonaka, K.; Masuma, R.; Hayakawa, Y.; Hanaki, H.; Kobayashi, Y.; Petersson, G. A.; Omura, S.; Shiomi, K. A. Cagacillins A and B Produced by Simplicillium Sp. FKI-5895: New Circumventors of Arbebacin Resistance in MRSA. Org. Lett. 2013, 15, 4678–4681.
3. Tulebi Bezmin Abadi, A.; Rizvanov, A. A.; Haertlé, T.; Blatt, N. L. World Health Organization Report: Current Status of Antibiotic Resistance. BioNanoScience 2019, 9, 778–788.
4. (a) Mepuro, Y.; Ito, J.; Nakagawa, K.; Kuwahara, S. Total Synthesis of the Broad-Spectrum Antibiotic Amycolamin. J. Am. Chem. Soc. 2022, 144, 2523–2527. (b) Wright, P. M.; Seiple, I. B.; Myers, A. G. The Evolving Role of Chemical Synthesis in Antibiotic Drug Discovery. Angew. Chem., Int. Ed. 2014, 53, 8840–8869.
5. Du, L.; Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. New Alkaloids and Diterpenes from a Deep Ocean Sediment Derived Fungus Penicillium Sp. F23-2. J. Nat. Prod. 2013, 76, 2106–2112.
6. (a) Li, C.; Johnson, R. P.; Porco, J. A. Total Synthesis of the Quinone Epoxide Dimer (+)-Torreynacid: Application of a Biomimetic Oxidation/Electrocyclization/Diels–Alder Dimerization Cascade. J. Am. Chem. Soc. 2003, 125, 5095–5106. (b) Jung, S. H.; Hwang, G.-S.; Lee, S. I.; Ryu, D. H. Total Synthesis of (+)-Ambuic Acid: a-Bromination with 1,2-Dibromomethanol. J. Org. Chem. 2012, 77, 2513–2518. (c) Labor, M.; Heguaburu, V. L.; Pandolfi, E. M.; Schapiro, V. Asymmetric Synthesis of a Model Compound for the Cyclohexenone Core of Amulic Acid. Tetrahedron: Asymmetry 2008, 19, 893–895. (d) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczyński, R. M.; Porco, J. A. Exploring Chemical Diversity of Epoxyquinoid Natural Products: Synthesis and Biological Activity of (−)-Jestereone and Related Molecules. Org. Lett. 2001, 3, 1649–1652. (e) Mehta, G.; Pan, S. C. A Total Synthesis of the Epoxyquinone Based Antifungal Natural Product (+)-Amulic Acid. Tetrahedron Lett. 2005, 46, 3045–3048. (f) Li, C.; Lobkovsky, E.; Porco, J. A. Total Synthesis of (+)-Torreynacid. J. Am. Chem. Soc. 2000, 122, 10484–10485. (g) Mehta, G.; Pan, S. C. Total Synthesis of the Novel, Biologically
Active Epoxyquinone Dimer (±)-Torreyanic Acid: A Biomimetic Approach. **Org. Lett.** **2004**, *6*, 3985−3988.

(8) (a) Pedersen, M. J.; Born, S.; Neuenschwander, U.; Skovby, T.; Mealy, M. J.; Kiil, S.; Dam-Johansen, K.; Jensen, K. F. Optimization of Grignard Addition to Esters: Kinetic and Mechanistic Study of Model Phthalide Using Flow Chemistry. **Ind. Eng. Chem. Res.** **2018**, *57*, 4859−4866. (b) Nicaise, O. J.-C.; Mans, D. M.; Morrow, A. D.; Hefti, E. V.; Palkovacs, E. M.; Singh, R. K.; Zukowska, M. A.; Morin, M. D. Stable Enols from Grignard Addition to 1,2-Diesters: Serendipity Rules. **Tetrahedron** **2003**, *59*, 6433−6443. (c) Yamazaki, T.; Terajima, T.; Kawasaki-Taskasuka, T. Unusual Reactions of Grignard Reagents toward Fluoroalkylated Esters. **Tetrahedron** **2008**, *64*, 2419−2424.

(9) Fetizon, M.; Golfier, M.; Mourgues, P.; Louis, J.-M. Silver Carbonate on Celite Oxidations. In: Oxidations. Organic Syntheses by Oxidation with Metal Compounds; Springer, 1986, pp. 503−567. DOI: 10.1007/978-1-4613-2109-5_10.

(10) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. Highly Chemoselective Oxidation of 1,5-Diols to δ-Lactones with TEMPO/BAIB. **Tetrahedron Lett.** **2003**, *44*, 57.

(11) Aïssa, C. Improved Julia−Kocienski Conditions for the Methylenation of Aldehydes and Ketones. **J. Org. Chem.** **2006**, *71*, 360−363.

(12) Catino, A. J.; Forslund, R. E.; Doyle, M. P. Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation. **J. Am. Chem. Soc.** **2004**, *126*, 13622−13623.

(13) Paquette, L. A.; Wang, T. Z.; Huu, V. N. Access to Naturally Occurring Cyclooctanoids by Two-Carbon Intercalation. Total Synthesis of (+)-Ceroplastol I. **J. Am. Chem. Soc.** **1993**, *115*, 1676−1683.

(14) Marwah, P; Lardy, H. A.; Process for effecting allylic oxidation using dicarboxylic acid imides and chromium reagents, US 6,384,251B1, 1999.

(15) Andrus, M. B.; Lashley, J. C. Copper Catalyzed Allylic Oxidation with Peresters. **Tetrahedron** **2002**, *58*, 845−866.

(16) Yu, J.-Q.; Corey, E. J. Diverse Pathways for the Palladium(II)-Mediated Oxidation of Olefins by Tert-Butylhydroperoxide. **Org. Lett.** **2002**, *4*, 2727−2730.

(17) Salmond, W. G.; Barta, M. A.; Havens, J. L. Allylic Oxidation with 3,5-Dimethylpyrazole. Chromium Trioxide Complex Steroidal Δ5-7-Ketones. **J. Org. Chem.** **1978**, *43*, 2057−2059.

(18) Chen, D. X.; Ho, C. M.; Rudy Wu, Q. Y.; Wu, P. R.; Wong, F. M.; Wu, W. Convenient Oxidation of Benzylic and Allylic Halides to Aldehydes and Ketones. **Tetrahedron Lett.** **2008**, *49*, 4147−4148.

(19) Adam, W.; Nestler, B. Hydroxy-Directed Regio-Diastereoselective Ene Reaction of Singlet Oxygen with Chiral Allylic Alcohols. **J. Am. Chem. Soc.** **1993**, *115*, 5041−5049.

(20) Davies, A. G. The Schenck Rearrangement of Allylic Hydroperoxides. **J. Chem. Res.** **2009**, 2009, 533−544.

(21) Kadam, S. T.; Kim, S. S. Catalyst-Free Silylation of Alcohols and Phenols by Promoting HMDS in CH3NO2as Solvent. **Green Chem.** **2010**, *12*, 94−98.

(22) Matsunaga, K.; Hirajima, H.; Kishida, A.; Takatori, K.; Nagaoka, H. Novel PDC Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols to β-Substituted Enones. **Tetrahedron Lett.** **2015**, *56*, 5941−5944.

(23) Ireland, R. E.; Liu, L. An improved procedure for the preparation of Dess-Martin periodinane. **J. Org. Chem.** **1993**, *58*, 2899.

(24) (a) Williams, J. D.; Kamath, V. P.; Morris, P. E.; Townsend, L. B. D-Ribonolactone and 2,3-Isopropylidene(D-ribonolactone). **Org. Synth.** **2005**, *82*, 75. (b) Suh, H.; Wilcox, C. S. Chemistry of F1,F0-ATPase Inhibitors. Stereoselective Total Syntheses of (+)-Citreoviridin and (−)-Citreoviridin. **J. Am. Chem. Soc.** **1988**, *110*, 470−481.

(25) Jana, S.; Sarpe, V. A.; Kulkarni, S. S. Total Synthesis of Emmuyguyacins A and B, Potential Fusion Inhibitors of Influenza Virus. **Org. Lett.** **2018**, *20*, 6938−6942. See SI for details