JOC The Journal of Organic Chemistry

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Syntheses of Papyracillic Acids: Application of the Tandem Chain Extension−Acylation Reaction

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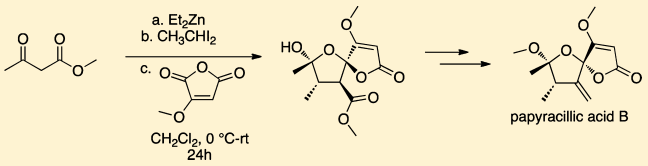
Supporting Information

ABSTRACT: A synthetic approach to the papyracillic acid family of natural products has been developed. The spiroacetal core is rapidly assembled through an unprecedented zinc carbenoid-mediated tandem chain extension−acylation reaction. Subsequent functional group manipulation provided access to papyracillic acid B and 4-*epi*-papyracillic acid C. The successful preparation of these molecules resulted in the clarification of structural assignments of members of this family of natural products.



INTRODUCTION

Papyracillic acid A (**1**), initially isolated from the ascomycete fungus *Lachnum papyraceum*,[1] possesses a spirofused cyclic ketal core (Figure 1) appended with an exocyclic alkene.

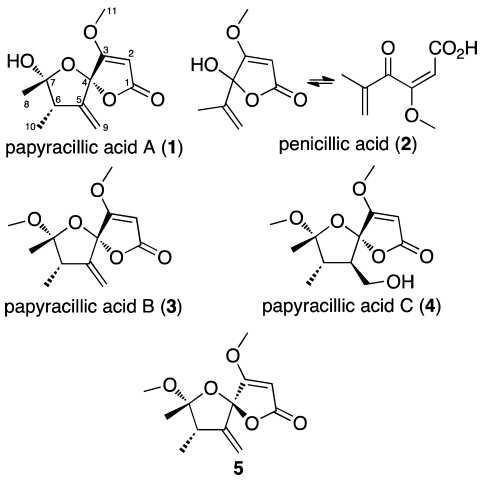


Figure 1. Papyracillic acids and analogous penicillic acid.

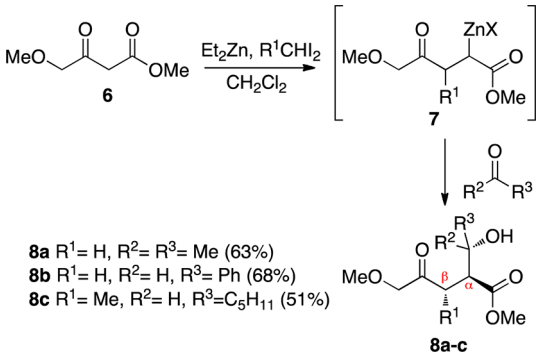
Structural similarities between papyracillic acid A (**1**) and the mycotoxin penicillic acid[2−4] (**2**) suggest an equilibrium relationship between hemiketal and open-chain isomers, a claim that was supported by the observation that papyracillic acid A (**1**) exists in solution as a 1:1:2:4 mixture of unspecified isomers. The cytotoxicity of papyracillic acid, also in analogy to penicillic acid,[5] was proposed to be due to its reactivity with bioavailable nucleophiles. In a subsequent study by Shan et al., the conjugate addition of a cysteine thiol functionality occurred at the exocyclic alkene (C-9), which further supported the assertion that the spiroketal of papyracillic acid A (**1**) exists in equilibrium with open-chain forms.[6]

More recently, compound **1**, along with two analogous papyracillic acids B (**3**) and C (**4**, Figure 1), were isolated from an endophytic fungus *Microsphaeropsis* sp., extracted from the branches of the tree *Larix decidua*, in Hjerting, Denmark.[7] The characterization of papyracillic acids B (**3**) and C (**4**) revealed an inconsistency in the stereochemical assignment of the quaternary spirofused carbon (C-4). Following the initial isolation of **1**, reported by Shan et al.,[1] the isomeric mixture was converted to methyl ketal **5** by treatment with methanol and trifluoroacetic acid. The relative stereochemistry of the major isomer was elucidated through 2D spectroscopic analysis, which produced an *R*,*R* stereochemical assignment at the quaternary carbon (C-4) and the ketal carbon (C-7). Later, Dai et al.[3] assigned the absolute stereochemistry of **1**, **3**, and **4** by comparison of TDDFT calculations and solid-state CD spectra, which resulted in an *S*,*R* stereochemical assignment at the spirofused quaternary center (C-4) and ketal carbon (C-7). Dai and co-workers also compared NMR spectra of papyracillic acid B (**3**) to that of the synthesized methyl ketal **5** reported by Shan and co-workers, and they concluded that the natural product **3** was epimeric to the semisynthetic spirofused methyl ketal **5** at the quaternary center (C-4) position. Herein, we report the first concise syntheses of papyracillic acids, which have resulted in clarification of the stereochemical assignment at the C-4 (spiro-carbon) position.

Our development of the carbenoid-mediated homologation of β-keto carbonyls to γ-keto carbonyls, referred to as the zinc-mediated chain extension reaction,[8] has resulted in variations that facilitate the incorporation of functionality at both the α-position[9−11] and β-position[12] of the γ-keto product. For example, when β-keto ester **6** was subjected to a zinc carbenoid derived from diethylzinc and diiodomethane (R^1 = H), an organometallic intermediate **7** (Scheme 1) was generated.[13] Similar to the Reformatsky dimer,[14,15] intermediate **7** can be

Received: August 17, 2012
Published: September 26, 2012

Scheme 1. Tandem Chain Extension−aldol Reaction

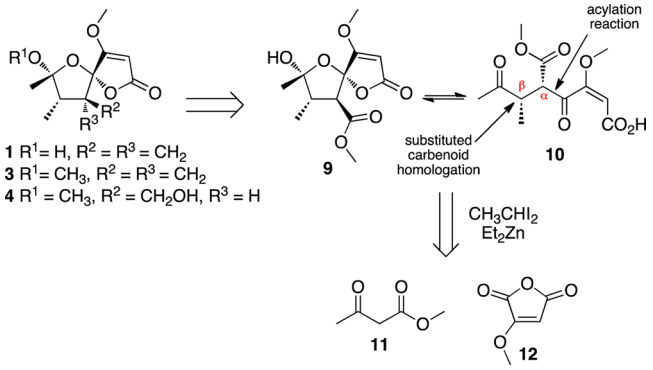


trapped with aldehydes or ketones to produce α-substituted aldol products (**8a** and **8b**). The regiospecific substitution at the α-position of a γ-keto substrate has been key to the synthesis of peptide isosteres[16] and natural products.[17,18] Regiospecific incorporation of a methyl substituent at the β-position has been achieved through use of a substituted carbenoid derived from diethylzinc and diiodoethane (R^1 = Me). Subsequent addition of an aldehyde to the organometallic intermediate generated the α,β-substituted γ-keto ester **8c**. The successful establishment of two consecutive stereocenters in one step inspired the synthetic approach to the papyracillic acids.

RESULTS AND DISCUSSION

We envisioned that establishment of the spirofused cyclic ketal core would be possible through one concise synthetic step, utilizing the zinc carbenoid homologation reaction (Scheme 2).

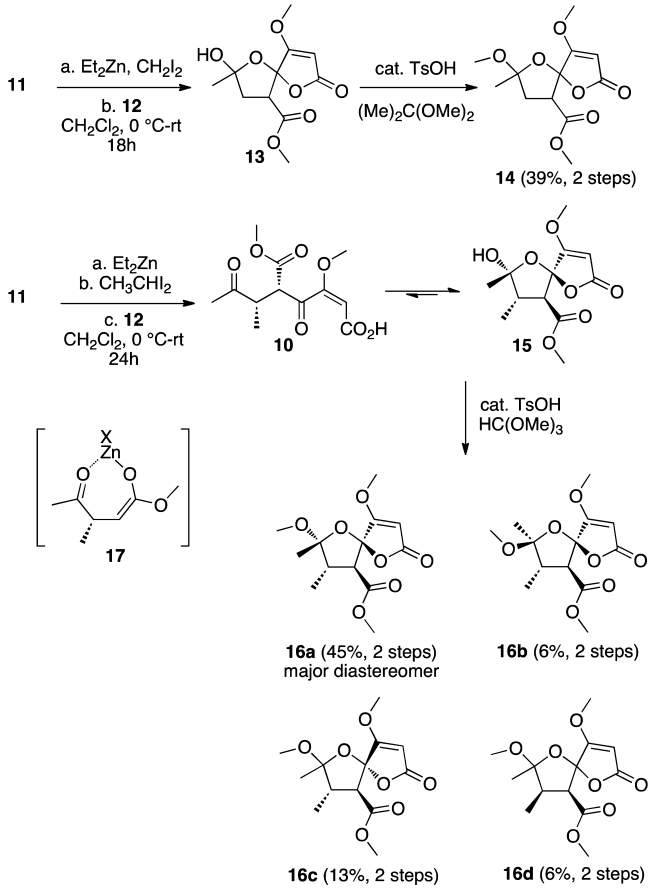
Scheme 2. Retrosynthetic Analysis for the Syntheses of Papyracillic Acids



Papyracillic acids would arise from hemiketal **9**, which would exist in equilibrium with open-chained isomer **10**. Inspection of isomer **10** reveals an α,β-substituted γ-keto ester suited to develop from the homologation of β-keto ester **11**. Capitalizing on the regiospecific anionic character generated at the α-position during the homologation of **11**, the addition of 3-methoxymaleic anhydride **12** was proposed to result in an acylation reaction to furnish the desired α-acyl-β-methyl-γ-keto ester **10**. While incorporation of a methyl substituent using a methyl-substituted carbenoid[12] was a well-established variant, the direct incorporation of an acyl group through the addition of an anhydride has not been reported.

The potential for utilization of anhydrides in a tandem reaction process for the production of spirofused cyclic ketal cores was explored by treatment of methyl acetoacetate (**11**) with the Furukawa-modified carbenoid,[19] followed by exposure of the resulting organometallic intermediate to 3-methoxymaleic anhydride[20] (**12**, Scheme 3). While the ^{1}H NMR spectrum

Scheme 3. Synthesis of (±)-Spirofused Cyclic Ketals



of the crude reaction mixture was challenging to interpret due to the equilibrium between hemiketal **13** and other isomeric forms, the ^{13}C NMR spectrum showed resonances consistent with hemiketals and ketals. The crude reaction mixture that contained hemiketal **13** was treated with dimethoxypropane in an effort to trap the spirofused ketal core as a product mixture suitable for chromatographic separation. Purification of the crude mixture resulted in the identification of three spirofused cyclic ketal diastereomers **14**. The successful preparation of ketals **14** confirmed the tandem chain extension−acylation reaction was suitable for the synthesis of spirofused ketal backbones present in the papyracillic acids; thus, the stereochemical assignments for ketals **14** were not pursued.

Incorporation of a methyl substituent into the spirofused ketal backbone arose from the homologation reaction using a zinc carbenoid derived from 1,1-diiodoethane[21] and diethylzinc (Scheme 3). Analysis by ^{1}H and ^{13}C NMR suggested that hemiketal **15** was the major isomer present in the crude reaction mixture, and the relative stereochemistry was eventually assigned through X-ray crystallographic analysis. The crude reaction mixture that contained hemiketal **15** was subjected to catalytic *p*-toluenesulfonic acid in trimethyl orthoformate, which produced methyl ketal **16a** as the major diastereomer after chromatographic purification. Previous studies directed toward the synthesis of *cis,cis*-phaseolinic acid

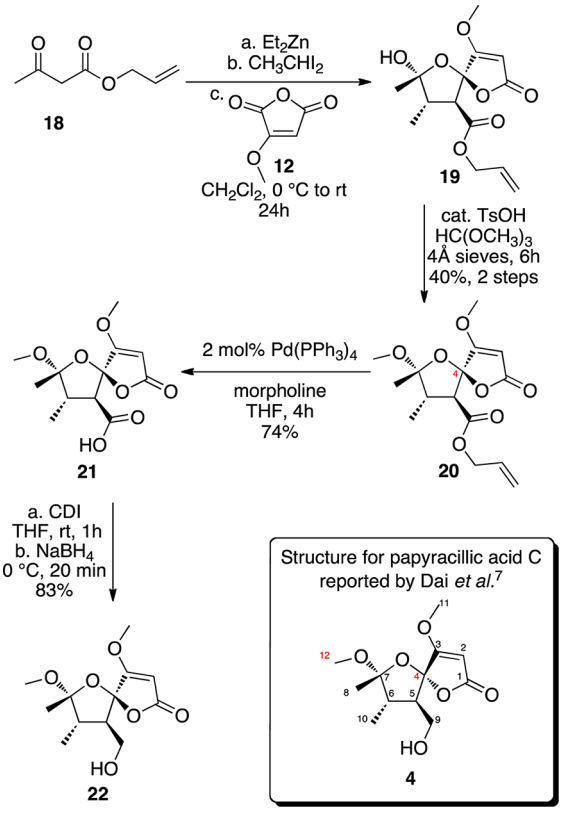
dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

revealed that a methyl group at the β-position influences the facial selectivity of enolate **17** in an aldol reaction. Upon the basis of similar facial selectivity in the acylation reaction, a cis relationship between the methyl and carboxyester would be predicted;[14] however, an unanticipated trans-stereochemical relationship between the methyl group (C-6) and the carboxyester functionality (C-5) was observed through the ^{1}H NMR coupling constant (^3J = 12.3 Hz) and confirmed by X-ray crystallographic analysis of **16a**. The trans-stereochemical relationship between the methyl and carboxyester substituent was hypothesized to arise via an epimerization of the α-stereocenter of open-chained isomer **10**. During the preparation of **16a**, several other stereoisomers were identified and isolated. The structure of **16b** was assigned on the basis of X-ray crystallographic analysis. The complete stereochemical assignments of **16c** and **16d** were not possible. On the basis of the vicinal coupling constant, the stereochemical relationship between the methyl substituent and the carboxymethyl substituent could be assigned. During the optimization of the reaction conditions, a *cis*-ketal diastereomer **16d** (^3J = 7.3 Hz) was identified, which prompted an investigation of the equilibration involving the cis and trans-substituted hemiketal diastereomers. A microwave-induced epimerization protocol that provided rapid and selective access to the desired *trans*-hemiketal diastereomers was developed; however, this method was only applied to methyl ester substrates. While the trans-relationship between the methyl and carboxyester required for the synthesis of papyracillic acid C (**4**) was now available in a selective fashion, the direct reduction of the methyl ester to the desired hydroxymethyl substituent was not successful.

Integration of an allyl-protected carboxylic acid facilitated conversion to the hydroxymethyl functionality found in papyracillic acid C (**4**, Scheme 4). Allyl acetoacetate (**18**) was exposed to a methyl-substituted carbenoid, and subsequent addition of **12** provided a complex mixture of isomers. NMR analysis of the crude reaction mixture allowed for hemiketal **19** to be identified as the major diastereomer. Acid-catalyzed conversion of the crude mixture of isomers, which contained **19**, produced a mixture of ketal diastereomers. After meticulous column chromatography separation, ketal **20** was obtained as the major diastereomer, and the stereochemistry was assigned on the basis of an X-ray crystal structure analysis, which showed a trans-relationship between the methyl substituent and allyl ester group. Interestingly, the relative stereochemistry at the quaternary center (C-4) of **20** was opposite to that of the papyracillic acids reported by Dai et al.[7] Ester **20** was converted to carboxylic acid **21** via mild palladium(0)-mediated deallylation reaction.[22,23] Subsequent reduction of **21**, mediated by in situ acyl imidizole formation and sodium borohydride reduction, furnished the spirofused cyclic ketal **22** with the desired hydroxymethyl functionality. Control of temperature in the reduction was important, for allowing the reaction to warm to room temperature resulted in degradation of the lactone ring.

Data for spirofused cyclic ketal **22** was compared to the data reported for papyracillic acid C (**4**). While illustrated in the original paper[7] as a methyl ketal, a closer look at the published ^{1}H NMR data for papyracillic acid C (**4**) revealed characterization data that was not consistent with a methyl ketal. For example, no methyl resonance was reported in the ^{1}H or ^{13}C NMR spectra for the methyl ketal. Furthermore, high-resolution electron ionization mass spectrometry (HRMS EI) was consistent with a hemiketal structure rather than a methyl

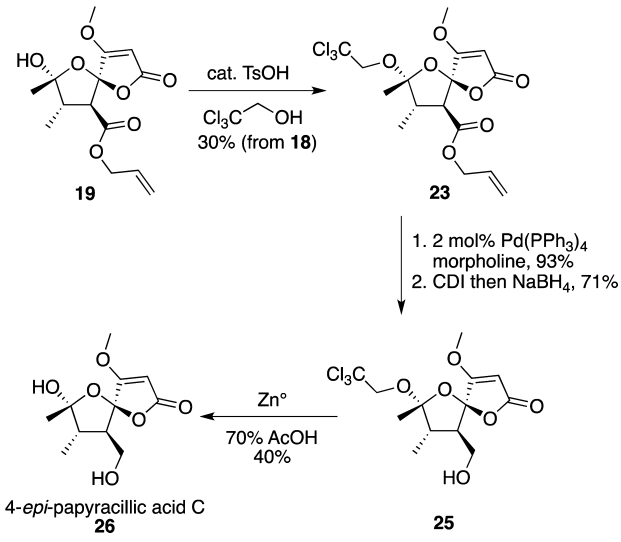
Scheme 4. Synthesis of Hydroxymethyl (±)-22



ketal. This evidence suggests the structure for papyracillic acid C (**4**) was incorrectly illustrated as a methyl ketal and should be reassigned as the hemiketal. Therefore, compound **22**, which possessed the same connectivity as the reported natural product, was neither papyracillic acid C nor an epimer.

Selective hydrolysis of methyl ketal **22** was not successful under standard hydrolysis conditions; thus, an alternative route was pursued. The trichloroethyl group has been reported as a protecting group for hemiketals.[24] Exposure of **19** to catalytic *p*-toluenesulfonic acid in trichloroethanol produced protected ketal **23** (Scheme 5). Deallylation and subsequent reduction of

Scheme 5. Synthesis of (±)-4-*epi*-Papyracillic Acid C (26)

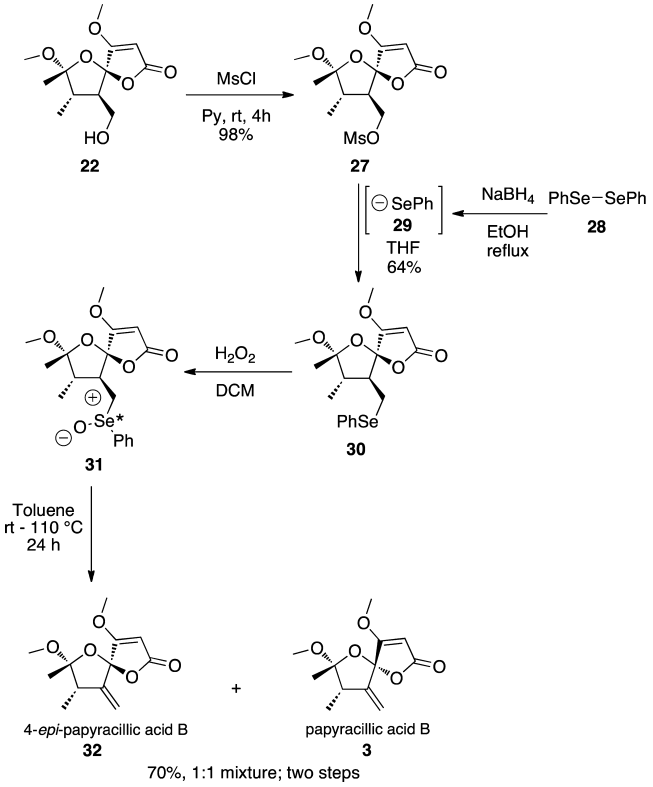


dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

the resulting carboxylic acid **24** resulted in the desired hydroxymethyl-furnished spirofused ketal **25**. Several different reaction conditions were surveyed for the removal of the trichloroethyl group. Finally, treatment of **25** with activated granular zinc in 70% acetic acid resulted in the liberation of hemiketal and preparation of 4-*epi*-papyracillic acid (**26**). A comparison of NMR data of **26** with that reported for papyracillic acid C revealed that the compounds were very similar, albeit not identical. The possibility exists that the two compounds are identical and that the stereochemistry of **4** was misassigned or that **26** was completely epimerized under the deprotection conditions. All attempts at equilibrating **26** to provide papyracillic acid C (**4**) were unfruitful, suggesting that either the spirofused hemiketal is kinetically inert or that **26** is thermodynamic stable.

Elimination of the hydroxymethyl substituent of **22** was hypothesized to give rise to the *exo*-cyclic alkene present in papyracillic acid B (**3**, Scheme 6). A series of unsuccessful

Scheme 6. Synthesis of (±)-4-*epi*-Papyracillic Acid B (32) and (±)-Papyracillic Acid B (3)



reactions were attempted, including a Grieco elimination,[25] mesylate displacement, and a xanthate ester pyrolysis, all of which resulted in the recovery of unreacted starting material. The close proximity to the quaternary center posed a challenge for functionalizing alcohol **22** through an S_N2 displacement; thus, **22** was treated with methenesulfonyl chloride in pyridine to produce mesylate **27**. Diphenyl diselenide (**28**) was reduced with sodium borohydride in ethanol to produce anion **29**,[26] which displaced mesylate **27** at room temperature. Purification by preparative thin layer chromatography allowed selenide **30** to be isolated as a single diastereomer, as evident by the ^{1}H and ^{13}C NMR spectra. Hydrogen peroxide-mediated oxidation of selenide **30** to selenoxide **31** was performed in an effort to induce syn-elimination of the selenoxide.[27] Although purification of selenoxide **31** was not conducted, the ^{1}H NMR spectrum of the crude product reveals a clean mixture of two selenoxide diastereomers. Selenoxide **31** was suspended in toluene and gradually warmed to refluxing temperature over the course of 24 h. In addition to the isolation of 4-*epi*-papyracillic acid B (**32**), a second diastereomer was isolated as part of a 1:1 mixture. Through comparison to the literature data reported by Dai et al.,[7] the second diastereomer was identified to be the natural product papyracillic acid B (**3**). Because the selenide **30** was isolated cleanly as a single diastereomer, epimerization of 4-*epi*-papyracillic acid B (**32**) to papyracillic acid B (**3**) is postulated to occur through the intermediacy of an allylic oxocarbenium ion made possible by the formation of the exo-cyclic methylene.

As previously mentioned, the structure for papyracillic acid B (**3**) reported by Dai et al.[7] was compared with one of the synthesized ketal isomers **3** (Figure 2). The ^{1}H NMR chemical

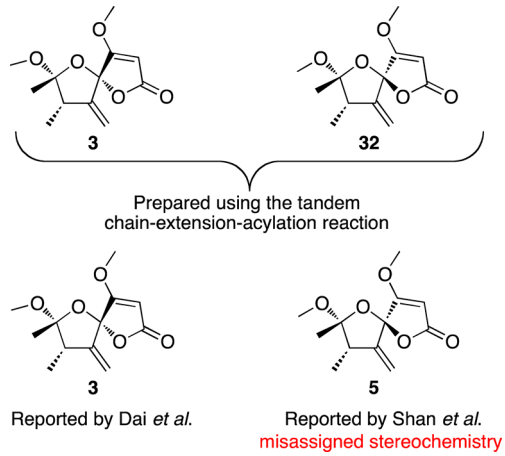


Figure 2. Stereochemical comparison.

shifts and coupling constants for **3** (reported and synthetic) were consistent, which suggests the compounds are identical and have the same relative stereochemistry. (For complete ^{1}H and ^{13}C NMR characterization data of **3** (synthetic), **3** (natural), **5**, and **32**, refer to the Supporting Information). Ketal **5**, prepared semisynthetically by Shan et al.,[1] had been assigned, on the basis of an HMBC and NOESY correlation study, a structure that is epimeric to that of naturally occurring papyracillic acid B (**3**) at the spirofused quaternary center. This assigned structure is identical to the **32**, which was prepared in the synthetic study described above. Comparison of the data reported by Shan et al. for ketal **5** with the data acquired for ketal **32**, synthesized through the chain extension−acylation reaction, revealed inconsistencies in both the ^{1}H and ^{13}C NMR spectra. Because the relative stereochemical configuration of **32** was rigorously assigned by X-ray crystallography, we conclude that the ketal **5** cannot be an epimer of papyracillic acid B (**3**) at C4 and that the structure of **5** was misassigned by Shan.

■ CONCLUSION

In summary, a tandem chain extension−acylation reaction was developed and successfully applied to the synthesis of spirofused cyclic ketals in two steps from readily available starting materials. Subsequent manipulation of the ketal backbone allowed for the first reported synthesis of papyracillic acids. The synthesis of 4-*epi*-papyracillic acid C and its methyl

dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

ketal precursor confirm that papyracillic acid C was misrepresented as the methyl ketal when, in fact, papyracillic acid C is a hemiketal. Papyracillic acid B and 4-*epi*-papyracillic were synthesized as a 1:1 mixture of epimers. Subsequent comparison of NMR data of the synthetic 4-*epi*-papyracillic acid B to a semisynthetic methyl ketal epimer (**5**) reported by Shan revealed a stereochemical misassignment of **5** in the original paper that reported isolation of papyracillic acid A. The successful regiospecific incorporation of an anhydride onto a γ-keto ester backbone has further broadened the scope of the zinc carbenoid-mediated chain extension reaction. The development of a nonracemic synthetic approach to these compounds and the application of this strategy to the formation of the cytotoxic agent papyracillic acid A are under investigation.

EXPERIMENTAL SECTION

General. All reagents were received from commercial sources and used as received. Anhydrous nitrogen gas was introduced into the reaction vessel through a Tygon tube with a needle or glass inlet adaptor. Anhydrous solvents were obtained by filtration through drying agent with nitrogen pressure. Tetrahydrofuran (THF) and dimethylformamide (DMF) were subsequently stored over 3 Å and 4 Å sieves, respectively. Preparative chromatography was accomplished through the use of silica gel GF 1000 μm with UV 254 glass-backed plates. Flash column chromatography was preformed with Silica-P Flash Silica Gel with 40−63 μm partial size. Mobile phases were freshly prepared as described in Detailed Procedures. Thin layer chromatography (TLC) analysis was conducted on glass-backed silica gel 60 Å 250 μm thickness with fluorescent indicator. TLC solvent systems were identical to the mobile phase used for column chromatography, unless otherwise specified. Nuclear magnetic resonance (NMR) spectroscopy was achieved using a spectrometer operating at 500 or 400 MHz for ^{1}H and at 126 or 100 MHz for ^{13}C spectroscopy. All carbon spectra were proton-decoupled. ^{1}H resonances were reported downfield relative to TMS (δ 0 ppm) reference, and ^{13}C resonances were referenced to $CDCl_3$ (δ 77.16 ppm) or acetone-d_6 (δ 206.26). The following abbreviations were used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad, app = apparent. High-resolution (TOF) mass spectra were measured using electrospray ionization. Infrared (IR) spectroscopy was conducted using an FTIR with diamond ATR probe.

Detailed Procedures. *3-Methoxymaleic Anhydride (**12**).* An oven-dried 25-mL round-bottom flask, equipped with magnetic stir bar, reflux condenser, and nitrogen gas inlet adapter, was charged with 2-methoxybut-2-enedioic acid (2.8 mmol, 0.41 g). Thionyl chloride (6 mL) was added directly to the flask via an oven-dried syringe whereupon bubbling occurred. The gaseous solution was stirred for 1 h at room temperature and then brought to reflux for 16 h. The solvent was removed by distillation under reduced pressure in a well-ventilated fume hood (30 mmHg, 50 °C) to afford a viscous orange oil. The crude product was purified by flash column chromatography, eluting with (4:1) hexane−ethyl acetate mobile phase (R_f = 0.3) to provide 3-methoxyfuran-2,5-dione **12** as an off-white solid (0.24 g, 66%) (mp 110−116 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.8, 160.8, 98.9, 60.6; IR (neat) ν 3126, 1856, 1763, 1639, 1454, 1438, 1340 cm^{-1}. HRMS (ESI) m/z calcd for $C_5H_5O_4$ (M + H$^+$) 129.0182, found 129.0191.

*Hemiketal **15**.* **Method A**: An oven-dried 100-mL round-bottomed flask, equipped with magnetic stir bar, rubber septum, and nitrogen gas inlet needle, was charged with anhydrous dichloromethane (18 mL) and then cooled to 0 °C in an ice−water bath. Neat diethylzinc (2.5 mmol, 0.26 mL, 0.31 g) was added in one portion using an oven-dried 25 cm needle. Methyl acetoacetate (1 mmol, 0.11 mL, 0.12 g) was added in one portion, and the reaction was stirred at 0 °C for 15 min. 1,1-Diiodoethane (3 mmol, 0.24 mL, 0.85 g) was added dropwise over the course of 30 s, after which the reaction was stirred for 90 min while warming to room temperature. TLC analysis indicated consumption of starting material (R_f = 0.49) and formation of the intermediate enolate (R_f = 0.54), eluting with a (1:1) hexane−ethyl acetate mobile phase. To the clear reaction mixture was added 3-methoxymaleic anhydride (1.1 mmol, 0.14 g), dissolved in anhydrous dichloromethane (2 mL), dropwise over the course of 3 min. The resulting yellow reaction mixture was stirred for 16 h at room temperature (ca. 21−25 °C). TLC analysis indicated consumption of intermediate enolate (R_f = 0.54) and development of product (R_f = 0.14−0.0, streak), eluting with a (1:1) hexane−ethyl acetate mobile phase. The reaction was quenched with 3 M hydrochloric acid (ca. 15 mL) and then extracted with ethyl acetate (4 × 15 mL). The organic layers were pooled, dried with anhydrous sodium sulfate (ca. 10 g), gravity filtered, and concentrated via rotary evaporator (10 mmHg, 30 °C) to afford the title compounds **15** as a brown foamy residue (0.26 g). The crude product was used without further purification. Characteristic proton resonances for the major isomer **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 3.89 (s, 3H), 3.59 (s, 3H), 3.38 (d, J = 12.4, 1H), 2.60 (dq, J = 12.4, 6.7 Hz, 1H), 1.50 (s, 3H), 1.10 (d, J = 6.7, 3H); all carbon resonances for crude reaction mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 212.0, 177.6, 177.2, 176.7, 176.4, 173.9, 171.5, 170.6, 170.5, 169.9, 169.7, 169.5, 169.3, 168.1, 163.6, 162.1, 110.8, 108.2, 107.9, 107.0, 106.1, 103.3, 103.0, 101.6, 101.4, 99.0, 96.1, 90.4, 89.4, 60.3, 60.1, 57.4, 56.5, 55.6, 54.3, 52.7, 52.5, 51.0, 45.7, 44.0, 42.9, 42.7, 42.6, 41.0, 40.8, 36.6, 29.8, 28.7, 28.7, 25.9, 24.8, 22.8, 20.9, 16.6, 15.8, 14.2, 12.4, 12.2; IR (neat) ν 3434, 3124−2954, 1742, 1644 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_7$ (M + Na$^+$) 295.0788, found 295.0803. **Method B**: Followed method A for the formation of title compound **15**. The reaction mixture was quenched with 3 M hydrochloric acid (ca. 15 mL) and extracted with diethyl ether (3 × 25 mL). The organic extracts were pooled and washed with 5% sodium bicarbonate solution (3 × 25 mL). The aqueous layers were cooled to 0 °C in an ice−water bath, acidified to pH 2 with 3 M hydrochloric acid, and extracted with diethyl ether (5 × 25 mL). The organic extracts were pooled, dried with sodium sulfate (ca. 15 g), gravity filtered, and concentrated via rotary evaporation (10 mmHg, 25 °C) to a light yellow solid. The crude product was recrystallized from dichloromethane to afford the title compound **15** as a clear crystalline solid (83 mg, 31%) (R_f = 0.15, (1:1) hexane−ethyl acetate mobile phase) (mp 142−145 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 5.32 (s, 1H), 3.99 (s, 3H), 3.61 (s, 3H), 3.45 (d, J = 12.4 Hz, 1H), 2.58 (dq, J = 12.4, 6.7 Hz, 1H), 1.52 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 176.9, 168.6, 168.0, 107.7, 106.8, 90.3, 59.7, 54.4, 51.6, 43.1, 25.6, 11.8.

*Methyl ketal **16a**.* A 50-mL round-bottomed flask, equipped with magnetic stir bar, rubber septum, and calcium sulfate drying tube, was charged with crude hemiketal **15** (0.75 mmol, 205 mg) dissolved in 2,2-dimethoxypropane (8 mL, 0.1 M). *p*-Toluenesulfonic acid (0.08 mmol, 14 mg) was added as a solid in one portion. The reaction was stirred at room temperature for 12 h. The crude reaction mixture was concentrated via rotary evaporation (10 mmHg, 30 °C) to afford the title compound **16** as a viscous dark brown oil (204 mg). The mixture of diastereomers were separated by flash column chromatography on silica, eluting with a gradient mobile phase of (5:1), (4:1), (3:1) hexane−ethyl acetate. *trans*-Ketal **16a** was obtained as a white crystalline solid in 95 mg, 45% (two steps) (R_f = 0.21, 3:1 hexane−ethyl acetate) (mp 152−153 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 1H), 3.97 (s, 3H), 3.66 (s, 3H), 3.42 (d, J = 12.3 Hz, 1H), 3.28 (s, 3H), 2.67 (dq, J = 12.3, 6.7 Hz, 1H), 1.49 (s, 3H), 1.13 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 168.8, 168.0, 109.8, 106.9, 90.2, 59.7, 54.1, 52.2, 49.2, 44.2, 19.7, 11.8; IR (neat) ν 3000−2850, 1768, 1740, 1646, 1602 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{18}NaO_7$ (M + Na$^+$) 309.0945, found 309.0952.

*Methyl Ketals **16b**, **16c**, and **16d**.* During the preparation of methyl ketal **16a**, three minor methyl ketal diastereomers were identified after flash column chromatography of the crude reaction mixture, eluting with a gradient mobile phase of (5:1), (4:1), (3:1) hexane−ethyl acetate:

dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

***trans*-Ketal 16b** was obtained as a white crystalline solid in 13 mg, 6% (two steps). Stereochemical assignment was based upon X-ray crystallographic analysis (R_f = 0.18, (3:1) hexane−ethyl acetate) (mp 144−148 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 1H), 3.96 (s, 3H), 3.68 (s, 3H), 3.37 (s, 3H), 3.18−2.98 (m, 2H), 1.33 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 169.0, 167.5, 113.1, 105.5, 90.7, 60.0, 54.9, 52.5, 50.1, 38.3, 21.3, 13.7; IR (neat) ν 3126, 2989, 2953, 2837, 1770, 1739, 1645 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{18}NaO_7$ (M + Na$^+$) 309.0945, found 309.0965.

***trans*-Ketal 16c** was obtained as a clear oil in 31 mg, 15% (two steps). The trans-stereochemical relationship was assigned on the basis of the ^3J = 12.0 Hz coupling constant. R_f = 0.15, (3:1) hexane−ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.56 (d, J = 12.0 Hz, 1H), 3.32 (s, 3H), 2.54 (dq, J = 12.0, 6.7 Hz, 1H), 1.44 (s, 3H), 1.12 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.8, 169.7, 109.7, 108.1, 89.7, 59.7, 56.5, 52.2, 49.5, 47.2, 18.9, 12.1; IR (neat) ν 3000−2850, 1772, 1744, 1648 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{18}NaO_7$ (M + Na$^+$) 309.0945, found 309.0968.

***cis*-Ketal 16d** was obtained as a light yellow solid in 13 mg, 6% (two steps). The cis-relationship between the methyl and the carboxymethyl groups is assigned on the basis of the ^3J = 7.3 Hz coupling constant. Other stereochemistry is unknown. R_f = 0.09, (3:1) hexane−ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (s, 1H), 4.03 (d, J = 7.3 Hz, 1H), 3.94 (s, 3H), 3.68 (s, 3H), 3.29 (s, 3H), 2.62 (pentet, J = 7.3 Hz, 1H), 1.45 (s, 3H), 1.24 (d, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 169.4, 168.1, 111.6, 107.2, 90.5, 59.8, 52.0, 50.6, 49.3, 43.9, 17.5, 11.9; IR (neat) 3000−2850, 1776, 1743, 1648, 1610 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{18}NaO_7$ (M + Na$^+$) 309.0945, found 309.0980.

Microwave-Mediated Epimerization of cis- to trans-Hemiketals. A 5-mL Pyrex microwave vial, equipped with magnetic stir bar, was charged with a crude mixture of hemiketals (0.37 mmol, 100 mg, brown viscous oil) in EtOAc (3 mL). Concentrated hydrochloric acid (1 drop) was added directly to the solution, and the microwave vial was sealed with a cap. The vial was inserted into the reactor and subjected to microwave irradiation at 100 °C for 1.5 h. The reaction mixture was washed with water (2 mL), dried with sodium sulfate (ca. 1 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 35 °C) to afford a light brown foam (99 mg, 99% mass recovered). ^{1}H NMR analysis was used to establish the diastereomeric ratio before and after microwave irradiation of the crude residue. ^{1}H NMR (400 MHz, $CDCl_3$) Before microwave irradiation, dr (trans:cis) 1:1: δ 3.38 (d, J = 12.4, 1H), 3.31 (d, J = 8.0 Hz, 1H); After microwave irradiation, only trans-diastereomer observed: δ 3.38 (d, J = 12.4, 1H).

*Hemiketal **19**.* An oven-dried, one-necked, 250-mL round-bottomed flask, equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet, was charged with dry dichloromethane (60 mL) and cooled to 0 °C in an ice−water bath. Neat diethylzinc (7.5 mmol, 0.93 g, 0.77 mL) was added in one portion via an oven-dried needle followed by slow addition of allyl 3-oxobutanoate **18** (3 mmol, 0.43 g, 0.41 mL) and stirred for 10 min. 1,1-Diiodoethane (7.5 mmol, 2.12 g, 0.60 mL) was added to the reaction via syringe over a 3 min period and stirred for 0.5 h while warming to room temperature. The reaction was cooled to 0 °C in an ice−water bath before diethylzinc (7.5 mmol, 0.93 g, 0.77 mL) was slowly added and stirring for 10 min. 1,1-Diiodoethane (7.5 mmol, 2.12 g, 0.60 mL) was added via syringe over a 3 min period, and the reaction was stirred under a bed of nitrogen for 2 h while allowing it to warm to room temperature. TLC indicated consumption of allyl acetoacetate (R_f = 0.61) and evidence for chain-extended intermediate (R_f = 0.56), eluting with a 1:1 hexane−ethyl acetate mobile phase. 3-Methoxymaleic anhydride (3.2 mmol, 0.39 g) dissolved in dry dichloromethane (4 mL) was added dropwise via syringe over the course of 5 min and stirred for 18 h at room temperature. The reaction was quenched with 3 M hydrochloric acid (30 mL) and extracted with ethyl acetate (5 × 40 mL). The combined organic layers were dried with sodium sulfate (ca. 20 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 30 °C) to afford a brown viscous oil (0.86 g, 100%). The title compound **19** was used without further purification. Characteristic proton resonances for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.00 (s, 3H), 3.48 (d, J = 12.4 Hz, 1H), 2.75−2.65 (m, 1H), 1.61 (s, 3H), 1.21 (d, J = 6.7 Hz, 3H); all carbon resonances for the crude product mixture: ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 177.2, 176.3, 176.1, 169.3, 168.7, 167.5, 167.1, 131.4, 131.2, 119.5, 119.4, 119.2, 110.7, 108.2, 107.9, 107.6, 106.9, 106.0, 90.6, 89.7, 66.5, 66,1, 66.0, 60.1, 56.4, 55.7, 55.0, 54.2, 45.6, 44.1, 42.8, 33.1, 33.0, 27.2, 26.0, 25.6, 24.8, 22.8, 16.7, 14.2, 12.3, 12.2, 10.9, 10.6, 10.5; IR (neat) ν 3399, 3124−2924, 1742, 1716, 1644, 1455 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{18}NaO_7$ (M + Na$^+$) 321.0945, found 321.0972.

*Allyl Ester **20**.* A 100-mL round-bottomed flask, equipped with a magnetic stir bar, rubber septum, nitrogen gas inlet, and 4 Å sieves, was charged with crude hemiketal **19** (3 mmol, 0.86 g) in trimethyl orthoformate (30 mL). *p*-Toluenesulfonic acid (0.05 mmol, 10 mg) was added as a solid in one portion, and the reaction was stirred for 4 h or until TLC analysis indicated consumption of hemiketal (R_f = 0.11) and evidence for product (R_f = 0.43), eluting with (1:1) hexane−ethyl acetate mobile phase. The mixture was vacuum filtered through a pad of basic alumina and magnesium sulfate (ca. 2 g) and then concentrated via rotary evaporation (10 mmHg, 30 °C) to afford a brown viscous residue (0.94 g). The major diastereomer was isolated by flash column chromatography on silica, eluting with a gradient mobile phase of (10:1), (8:1), (5:1), (4:1) hexane−ethyl acetate. *trans*-Major diastereomer **20** was obtained as a viscous clear oil 375 mg, 40% (two steps) (R_f = 0.15, (4:1) hexane−ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.2, 10.5, 5.9 Hz, 1H), 5.27 (dq, J = 17.2, 1.5 Hz, 1H), 5.23 (dq, J = 10.4, 1.2 Hz, 1H), 5.11 (s, 1H), 4.56 (m, 2H), 3.96 (s, 3H), 3.44 (d, J = 12.3 Hz, 1H), 3.28 (s, 3H), 2.69 (dq, J = 12.2, 6.7 Hz, 1H), 1.50 (s, 3H), 1.14 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 176.7, 168.8, 167.3, 131.6, 119.0, 109.9, 107.1, 90.5, 66.0, 59.8, 54.2, 49.3, 44.2, 19.9, 11.8; IR (neat) ν 2989−2838, 1783, 1744, 1647, 1457, 1373 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{20}NaO_7$ (M + Na$^+$) 335.1101, found 335.1119.

*Carboxylic Acid **21**.* A 20-mL scintillation vial, equipped with stir bar, rubber septum, and nitrogen gas inlet, was charged with allyl ester **20** (0.81 mmol, 254 mg) in anhydrous tetrahydrofuran (6 mL). Morpholine (8.13 mmol, 0.71 mL) was added via syringe followed by tetrakis(triphenylphospine)palladium(0) (2 mol %, 19 mg), which was added in one portion as a yellow solid. The reaction was stirred for 4 h or until TLC analysis showed starting material (R_f = 0.41) was consumed and product (R_f = 0.19−0.0, streak) was observed, eluting with (1:1) hexane−ethyl acetate mobile phase. The solvent was removed via rotary evaporation (10 mmHg, 30 °C) to afford an orange residue that was dissolved in dichloromethane (5 mL). The organic layer was washed with 2 M hydrochloric acid (3 × 5 mL), dried with magnesium sulfate (ca. 2 g), vacuum filtered through a pad of Celite, and concentrated (10 mmHg, 25 °C) to afford an orange foam. The crude solid was suspended in dichloromethane (5 mL) and extracted with saturated sodium bicarbonate (3 × 2 mL). The aqueous layer was washed with dichloromethane (5 mL), cooled in an ice−water bath to 0 °C, acidified with dropwise addition of concentrated hydrochloric acid to pH 2, and extracted with ethyl acetate (5 × 5 mL). The organic layers were pooled, dried with magnesium sulfate (ca. 4 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 30 °C) to afford the title compound **21** as a white solid (186 mg, 84%) (mp 178−179 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 1H), 3.97 (s, 3H), 3.47 (d, J = 12.3 Hz, 1H), 3.28 (s, 3H), 2.65 (dq, J = 12.3, 6.7 Hz, 1H), 1.49 (s, 3H), 1.14 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 172.2, 169.5, 110.0, 107.0, 90.7, 60.0, 54.0, 49.3, 44.2, 19.8, 11.8; IR (neat) ν 3124, 2989−2944, 1751, 1647 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_7$ (M + Na$^+$) 295.0788, found 295.0808.

*Allyl Ester **23**.* A 20-mL scintillation vial, equipped with magnetic stir bar, rubber septum, and calcium sulfate drying tube, was charged with crude hemiketal **19** (0.53 mmol, 0.15 g), 2,2,2-trichloroethanol (0.80 mmol, 0.12 g, 0.08 mL), and toluene (5 mL). *p*-TsOH (0.05 mmol, 0.01 g) was added in one portion as a solid, and the reaction was stirred at room temperature for 48 h. The reaction was concentrated via rotary evaporation (10 mmHg, 40 °C), affording a black viscous oil. The crude residue was purified by preparative thin

dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

layer chromatography on silica, eluting with a (1:1) hexane−ethyl acetate mobile phase (R_f = 0.57). The title compound **23** was obtained as a white crystalline solid (68 mg, 30%) (mp 104−106 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.24 (dq, J = 10.4, 1.2, 1H), 5.14 (s, 1H), 4.63−4.52 (m, 2H), 4.15 (d, J = 10.5 Hz, 1H), 4.06 (d, J = 10.5 Hz, 1H), 3.95 (s, 3H), 3.56 (d, J = 12.3 Hz, 1H), 2.79 (dq, J = 12.3, 6.7 Hz, 1H), 1.60 (s, 3H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 168.5, 166.9, 131.5, 119.3, 109.9, 107.3, 96.7, 90.7, 74.5, 66.2, 59.8, 54.0, 44.6, 20.8, 11.8; IR (neat) ν 3125, 2988−2884, 1787, 1746, 1650 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{19}Cl_3NaO_7$ (M + Na$^+$) 451.0089, found 451.0100.

Carboxylic Acid ***24***. A 20-mL scintillation vial, equipped with magnetic stir bar, rubber septum, and nitrogen gas inlet needle, was charged with allyl ester **23** (0.76 mmol, 324 mg) in dry tetrahydrofuran (6 mL). Morpholine (7.6 mmol, 0.67 mL) was added in one portion via syringe, and the reaction was purged with nitrogen. Tetrakis(triphenylphospine)palladium(0) (2 mol %, 18 mg) was added in one portion as a solid, and the reaction was stirred for 3 h at room temperature under nitrogen. A solution of 1 M hydrochloric acid (6 mL) was added and extracted with ethyl acetate (4 × 8 mL). The organic layers were pooled, washed with 1 M hydrochloric acid (2 × 6 mL), dried with sodium sulfate (ca. 5 g), vacuum filtered, and concentrated in vacuo (10 mmHg, 30 °C) to afford a light brown crystalline solid. The solid was suspended in dichloromethane (ca. 15 mL) and washed with saturated sodium bicarbonate (3 × 10 mL). The aqueous layer was cooled in an ice−water bath to 0 °C, acidified with dropwise addition of concd hydrochloric acid to pH 2, and extracted with ethyl acetate (5 × 20 mL). The organic layers were pooled, dried with sodium sulfate (ca. 15 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 30 °C) to afford the title compound **24** as a white solid (275 mg, 93%) (mp 196−198, decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (s, 1H), 4.15 (d, J = 10.1 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H), 3.96 (s, 3H), 3.58 (d, J = 12.3 Hz, 1H), 2.74 (dq, J = 12.3, 6.7 Hz, 1H), 1.60 (s, 3H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 171.7, 169.1, 109.9, 107.2, 96.6, 90.9, 74.6, 59.9, 53.7, 44.6, 20.7, 11.7; IR (neat) ν 3130, 3005−2877, 1748, 1725, 1648, 1454 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{15}Cl_3NaO_7$ (M + Na$^+$) 410.9776, found 410.9789.

Hydroxymethyl ***25***. A 20-mL scintillation vial, equipped with magnetic stir bar, rubber septum, and nitrogen gas inlet needle, was charged with carboxylic acid **24** (0.60 mmol, 223 mg) in tetrahydrofuran (6 mL). Carbonyldiimidazole (0.63 mmol, 102 mg) was added as a solid in one portion and stirred at room temperature for 2 h. The reaction was cooled to 0 °C in an ice−water bath, sodium borohydride (1.98 mmol, 75 mg) was added in one portion as a solid, and the reaction was stirred for 30 min. TLC analysis indicated full consumption of the carboxylic acid starting material (R_f = 0.0−0.2, streak) and production of product (R_f = 0.75) eluting with an ethyl acetate mobile phase. A solution of 1 M hydrochloric acid (6 mL) was cautiously added at 0 °C and extracted with ethyl acetate (3 × 8 mL). The organic layers were pooled, washed with saturated sodium bicarbonate (2 × 8 mL), dried with sodium sulfate (ca. 3 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 30 °C) to afford a the title compound **25** white foam (158 mg, 71%), which did not require further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (s, 1H), 4.16 (d, J = 10.5 Hz, 1H), 4.04 (d, J = 10.5 Hz, 1H),3.91 (s, 3H), 3.73 (broad d, J = 6.1 Hz, 2H), 2.79 (dt, J = 11.6, 6.1 Hz, 1H), 2.29 (dq, J = 11.6, 6.7 Hz, 1H), 1.57 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 169.5, 109.8, 109.5, 96.9, 89.7, 74.5, 59.7, 59.0, 49.9, 44.3, 21.0, 11.3; IR (neat) 3456, 3127, 2987, 2939, 2882, 1758, 1644, 1456 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{17}Cl_3NaO_6$ (M + Na$^+$) 396.9983, found 397.0013.

*4-epi-Papyracillic Acid C (****26****)*. A 20-mL scintillation vial, equipped with magnetic stir bar, was charged with trichloroethyl ketal **25** (0.02 mmol, 7 mg) in 70% acetic acid (0.5 mL). Freshly activated zinc granular 20 mesh (14 mg) was added in one portion, and the heterogeneous reaction was stirred vigorously for 24 h at room temperature. The aqueous reaction mixture was extracted with ethyl acetate (5 × 1 mL). The organic layers were pooled, dried with sodium sulfate (ca. 1 g), vacuum filtered, and concentrated via rotary evaporation (10 mmHg, 30 °C) to afford light yellow residue. The crude product was purified by preprative thin layer chromatography on silica, eluting with an ethyl acetate mobile phase (R_f = 0.4). The title compound **26** was obtained as a clear solid (2 mg, 40%) as a mixture of isomers. ^{1}H and ^{13}C data reported for only the major hemiketal **26** isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (s, 1H), 3.94 (s, 3H), 3.74 (d, J = 5.1 Hz, 2H), 2.61 (dt, J = 12.6, 5.4 Hz, 1H), 2.28 (dq, J = 12.6, 6.7 Hz, 1H), 1.58 (s, 3H), 1.12 (d, J = 6.8, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 169.3, 109.1, 107.8, 89.9, 60.0, 59.1, 50.4, 42.4, 26.2, 11.9; IR (neat) 3380, 3125, 2925, 2854, 1750, 1641, 1456 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{16}NaO_6$ (M + Na$^+$) 267.0839, found 267.0876.

Mesylate ***27***. A 20-mL scintillation vial, equipped with magnetic stir bar, rubber septum, and a nitrogen gas inlet, was charged with carboxylic acid **21** (0.21 mmol, 57 mg) in dry THF (2 mL). Carbonyldiimidazole (0.23 mmol, 37 mg) was added in one portion, and the reaction was allowed to stir at room temperature for 1 h. The reaction was cooled to 0 °C in an ice−water bath, and sodium borohydride (0.69 mmol, 26 mg) was added in one portion. The reaction was allowed to stir to warm to room temperature for 30 min or until TLC analysis indicated evidence for product (R_f = 0.48), eluting with an ethyl acetate mobile phase. [The acyl imidazole intermediate decomposed rapidly on the silica TLC plate resulting in a streak (R_f = 0.0−0.78)]. The reaction was quenched with cautious addition of 1 M hydrochloric acid (2 mL) and extracted with ethyl acetate (3 × 3 mL). The organic layers were pooled, dried with sodium sulfate (ca. 2 g), vacuum filtered, and concentrated in vacuo (10 mmHg, 21 °C) to afford a viscous yellow oil. The crude oil was purified by preparative thin layer chromatography on silica, eluting with an ethyl acetate mobile phase (R_f = 0.48) to afford hydroxymethyl **22** as a white solid (45 mg, 83%) (mp 134−136 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (s, 1H), 3.93 (s, 3H), 3.71 (br d, J = 5.2 Hz, 2H), 3.29 (s, 3H), 2.64 (dt, J = 12.4, 5.2 Hz, 1H), 2.25 (dq, J = 12.4, 6.8 Hz, 1H), 1.76 (br s, 1H), 1.48 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 169.4, 109.8, 109.6, 89.7, 59.8, 59.0, 50.2, 49.3, 43.6, 20.2, 11.4; IR (neat) ν 1365, 2988−2854, 1763, 1644 cm^{-1}.

A 20-mL scintillation vial, equipped with magnetic stir bar, rubber septum, and nitrogen gas inlet, was charged with hydroxymethyl **22** (0.17 mmol, 44 mg) in pyridine (2 mL). Methanesulfonyl chloride (0.15 mmol, 22 mg) was added dropwise, and the reaction was stirred at room temperature for 2 h. A second portion of methanesulfonyl chloride (0.15 mmol, 22 mg) was added to the reaction mixture and then stirred for an additional 2h. The reaction was cooled to 0 °C in an ice−water bath and then quenched with 1 M hydrochloric acid (4 mL) and extracted with ethyl acetate (3 × 2 mL). The organic layers were combined, dried with sodium sulfate (ca. 2 g), vacuum filtered, and concentrated to a viscous yellow oil (56 mg, 95%). The title compound **27** was carried on without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.32 (dd, J = 10.2, 4.7 Hz, 1H), 4.21 (app t, J = 9.9 Hz, 1H), 3.94 (s, 3H), 3.29 (s, 3H), 2.99 (m, 1H), 2.95 (s, 3H), 2.10 (dq, J = 12.5, 6.8 Hz, 1H), 1.47 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 169.4, 109.6, 107.7, 89.6, 67.6, 59.9, 49.3, 47.8, 44.9, 37.2, 20.0, 11.5; IR (neat) ν 2979−2851, 1769, 1646, 1455, 1376 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{20}NaO_8S$ (M + Na$^+$) 359.0771, found 359.0775.

Selenide ***30***. A 5-mL round-bottomed flask, equipped with magnetic stir bar, relux condenser, rubber septum, and nitrogen gas inlet needle, was charged with diphenyl diselenide (0.13 mmol, 41 mg) in ethanol (1 mL). Sodium borohydride (0.15 mmol, 5.7 mg) was added cautiously as a solid, and the reaction was reluxed for 30 min at which time the solvent was removed via rotary evaporation (10 mmHg, 25 °C). The resulting light yellow solid was charged with mesylate **27** (0.12 mmol, 40 mg) in tetrahydrofuran and stirred for 5 h at room temperature. TLC indicated a mixture of selenide (R_f = 0.61) and mesylate (R_f = 0.26), eluting with (1:2) hexane−ethyl acetate mobile phase. A second batch of phenyl selenide anion (0.13 mmol, 41 mg) was prepared following the same procedure described above. The reaction mixture was transferred directly to the flask containing the second portion of phenyl selenide anion and allowed to stir at room

dx.doi.org/10.1021/jo3017617 | J. Org. Chem. 2012, 77, 9171−9178

temperature for 18 h. The solvent was removed via rotary evaporation (10 mmHg, 25 °C), the residue was partitioned between ethyl acetate (1 mL) and water (1 mL), and then the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The organic layers were pooled, dried with sodium sulfate (ca. 1 g), vacuum filtered, and concentrated to an orange viscous oil. The crude residue was purifed by preprative thin layer chromatography on silica, eluting with a (1:2) hexane−ethyl acetate mobile phase (R_f = 0.61). The title compound **30** was obtained as an off-white oil (30 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1H), 7.27−7.24 (m, 3H), 5.08 (s, 1H), 3.88 (s, 3H), 3.25 (s, 3H), 3.00 (dd, J = 12.6, 4.2 Hz, 1H), 2.91 (dd, J = 12.6, 9.6 Hz, 1H), 2.76 (ddd, J = 12.1, 9.6, 4.2 Hz, 1H), 2.07 (dq, J = 12.1, 6.8 Hz, 1H), 1.45 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 169.7, 132.5, 131.6, 129.3, 127.2, 109.2, 108.9, 90.7, 59.6, 49.3, 48.8, 48.2, 23.9, 20.4, 11.5; IR (neat) 3124, 2985, 2940, 2834, 1769, 1645, 1579, 1477 cm^{-1}. HRMS (ESI) m/z calcd for $C_{18}H_{22}NaO_5Se$ (M + Na$^+$) 421.0526, found 421.0512.

*4-epi-Papyracillic Acid B (**32**) and Papyracillic Acid B (**3**).* A 5-mL round-bottomed flask, equipped with magnetic stir bar, rubber septum, and thermalcouple, was charged with selenide **30** (0.06 mmol, 24 mg) in dichloromethane (0.4 mL). The solution was cooled to 0 °C in an ice−water bath and charged with a solution of 30% hydrogen peroxide (14.3 μL) and water (12.3 μL). The ice−water bath was removed, and the reaction was stirred for 15 min at room temperature, cooled to 0 °C, and stirred for an additional 15 min. The reaction mixture was diluted with dichloromethane (1 mL) and washed with saturated sodium bicarbonate (2 × 1 mL). The organic layer was dried with sodium sulfate (ca. 1 g), vacuum filtered, and concentrated (40 mmHg, 21 °C) to a light orange residue. The residue was suspended in toluene and stirred for 18 h at room temperature and then heated slowly to 110 °C over the course of 6 h. The solvent was removed in vacuo (10 mmHg, 35 °C) to afford a viscous orange oil (22 mg). The crude residue was purified by preparative thin layer chromatography on silica, eluting with hexane followed by (1:1) hexane−ethyl acetate (R_f = 0.71), to afford a 1:1 mixture of 4-*epi*-papyracillic acid B (**32**) and papyracillic acid B (**3**) as a viscous clear oil (10 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) 4-*epi*-papyracillic acid B (**32**) δ 5.22 (s, 1H), 5.13−5.11 (m, 2 H), 3.93 (s, 3H), 3.29 (s, 3H), 2.89−2.83 (m, 1H), 1.56 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H); papyracillic acid B (**3**) δ 5.22−5.18 (m, 2H), 5.07 (s, 1H), 3.87 (s, 3H), 3.31 (s, 3H), 2.71−2.66 (m, 1H), 1.51 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H); all carbon resonances for **32** and **3** ^{13}C (500 MHz, $CDCl_3$) δ 178.2, 176.7, 170.3, 169.1, 148.8, 148.5, 110.0, 109.4, 109.4, 109.0, 107.6, 107.2, 91.3, 88.6, 59.8, 59.7, 49.6, 49.5, 48.8, 46.2, 20.1, 19.0, 10.7, 9.9. IR (neat) ν 2923, 2853, 1767, 1642, 1455 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_5$ (M + Na$^+$) 263.0890, found 263.0908.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR data for compounds **12**, **15**, **16a−d**, **19−27**, **30**, and **32** and X-ray data for compounds **15**, **16a**, **16b**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Jon Briggs and Prof. Glen P. Miller for performing the X-ray crystallographic analysis. We acknowledge the NIH (R15 GM060967-02) for financial support.

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