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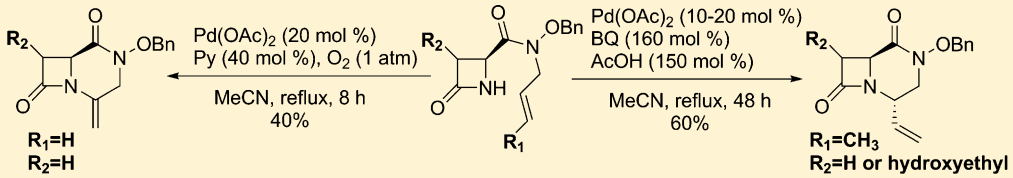
Syntheses of Hydroxamic Acid-Containing Bicyclic β-Lactams via Palladium-Catalyzed Oxidative Amidation of Alkenes

Maria O. Jobbins and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556, United States

Supporting Information



ABSTRACT: Palladium-catalyzed oxidative amidation has been used to synthesize hydroxamic acid-containing bicyclic β-lactam cores. Oxidative cleavage of the pendant alkene provides access to the carboxylic acid in one step.

INTRODUCTION

Human life expectancy increased dramatically with the advent of antibiotics.[1] However, because of the extensive use (and often overuse) of antibiotics as well as an innovation gap in antibiotic research, common infections are once again becoming deadly.[2] There is a great need for continued research in antibiotics.[3] β-Lactam antibiotics have been on the market since penicillin was introduced in the 1940s. This class of antibiotics has been kept viable by extensive structure−activity relationship (SAR) studies on the side chains and, to a lesser extent, on the bicyclic core (Figure 1).

Gram-negative pathogens are especially resistant to β-lactam antibiotics and β-lactamase inhibitors, as their arsenal of resistance mechanisms includes a highly impermeable cell wall. In order to overcome this barrier, there has been an interest in developing both bicyclic and monocyclic β-lactams with iron-chelating moieties[4−6] (Figure 2). These compounds have increased potency that is hypothesized to be due to active transport by the cell's iron uptake pathways.

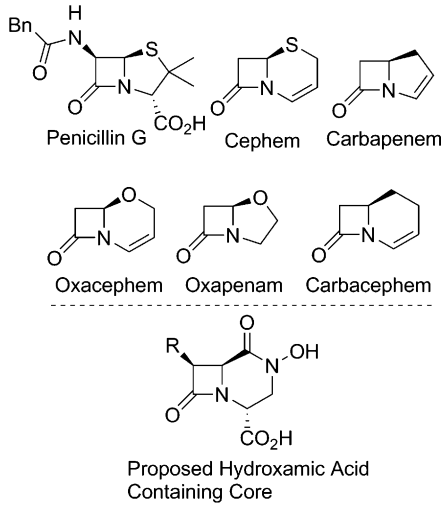


Figure 1. Penicillin G and representative antibiotic core structures.

The penicillin and cephalosporin cores can be obtained through biosyntheses and semisyntheses. However, access to the carbapenem core is less biosynthetically amenable. Therefore, significant effort has focused on the development of effective syntheses of this highly strained bicyclic core. Durst investigated various approaches to electrophilically activate alkenes and found that I_2 and $Hg(OAc)_2$ worked reasonably well on unfunctionalized systems[7] such as **2** to give **3** (Scheme 1). Kametani utilized an electrophilic cyclization approach with pendant alkenes and phenylsulfenyl chloride to give the carbapenem scaffold **4** in fair yield. However, this approach gave low yields for more highly functionalized systems.[8] Johnson further elaborated on Durst's results and showed that I_2 and propylene oxide gave a reproducible though modest yield of **5**.[9]

Transition-metal-catalyzed methods have also been employed. Kozawa and Mori[10] showed that propargyl carbonates, when treated with Pd(0), give the unsaturated bicyclic β-lactam system **7** (Scheme 2). They also showed that vinylic halides can be cyclized onto the lactam nitrogen with Pd(0).[11] Later, Xu demonstrated that Cu(I)-catalyzed couplings with vinylic halides can be used to access highly functionalized carbapenems **10**.[12] Additionally, cyclization with pendant allenes has been observed by Liebeskind with Pd(II),[13] Hiemstra with Pd(0),[14] and Seomoon with Au(III)[15] (Scheme 3).

Palladium-catalyzed oxidative amidation of alkenes has developed into a general way to make nitrogen-containing heterocycles, with the best results being obtained from intramolecular cyclizations and less basic (i.e., acylated or

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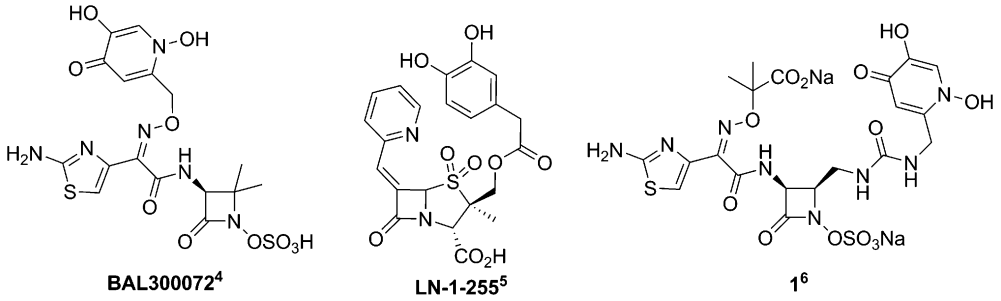
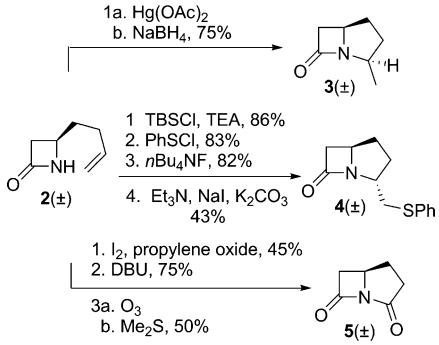
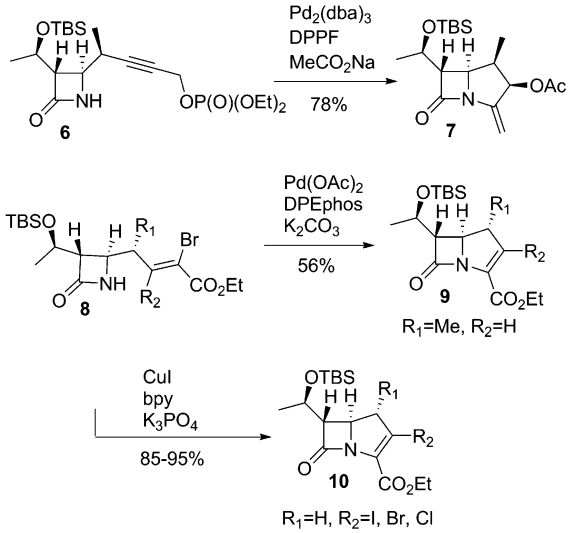


Figure 2. β-Lactam antibiotics with iron-binding functionality.

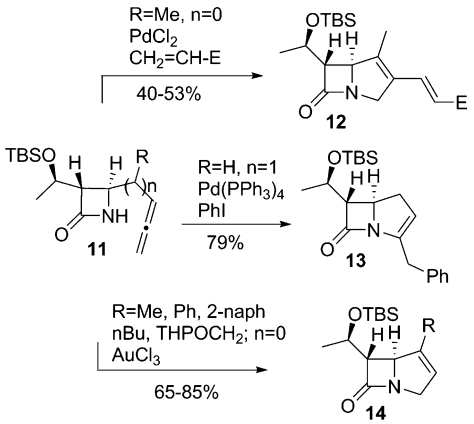
Scheme 1. Precedented Electrophilic Cyclizations onto the β-Lactam Nitrogen



Scheme 2. Transition-Metal-Catalyzed Cyclizations



Scheme 3. Precedented Cyclizations with Allenes



transport or a handle for further functionalization, such as the addition of iron-chelating side chains. To access this core, we hypothesized that pendant alkenes could provide appropriate substrates for palladium-catalyzed oxidative amidation. The resulting core would contain an alkene that could be further functionalized to give the ionizable carboxylic acid moiety (Figure 3).

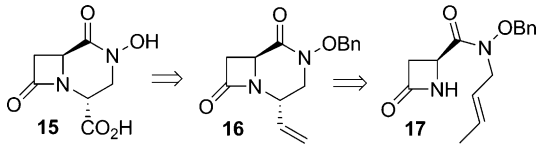


Figure 3. Partial retrosynthetic plan for the generation of hydroxamic acid-containing bicyclic β-lactams.

tosylated) nitrogens.[16] The transformation involves Pd(II)-catalyzed aminopalladation of the alkene to form the C−N bond and, upon β-hydride elimination, generation of an alkene and Pd(0). Pd(II) is then regenerated with an oxidant such as O_2/DMSO, O_2/pyridine, Cu(II)/O_2, or benzoquinone (BQ).[17]

Although decades of extensive studies were focused on modification of peripheral substituents and the core components of β-lactams in efforts to generate new antibiotics, modern methodologies could facilitate the generation of new variants that might provide opportunities for overcoming continuously evolving resistance problems. Here we report on our interest in expanding the known SAR of bicyclic β-lactams by including a hydroxamic acid moiety directly into the fused ring. This could provide a point for iron-chelate-mediated

■ RESULTS AND DISCUSSION

As shown in Scheme 4, the construction of functionalized monocyclic β-lactams **17a** and **17b**, which was necessary for testing the metal-mediated formation of the targeted bicyclic β-lactams, required the preparation of two key components: an appropriately functionalized hydroxylamine **20** and 4-carboxy-2-azetidinone (**23**). Thus, *N*-Boc-*O*-benzylhydroxylamine was alkylated with allyl bromide and crotyl bromide to give **19a** and **19b**, respectively, in excellent yields. The products were deprotected with TFA, and the free hydroxylamines were treated with conc. HCl to give salts **20a** and **20b**.[18,19] β-Lactam carboxylic acid **23** was synthesized from L-aspartic acid in four steps using literature precedent.[20] The β-lactam and hydroxylamines were then coupled using EDC·HCl to give **17a** and **17b**.

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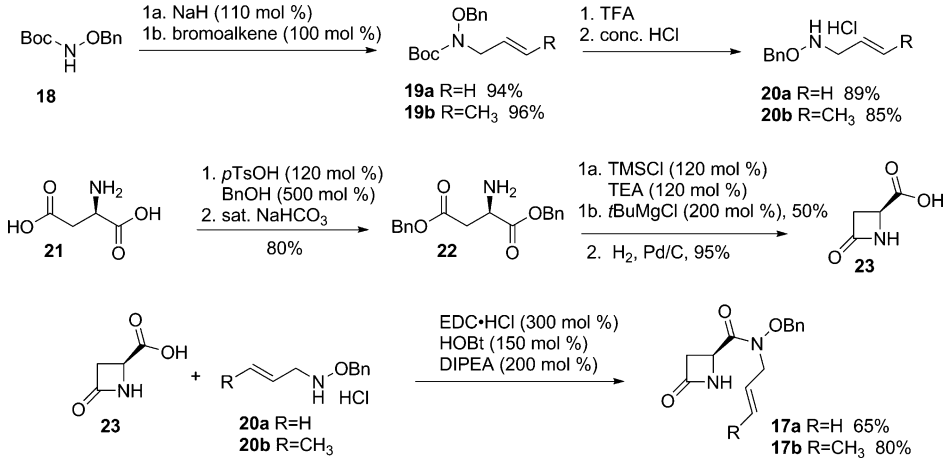
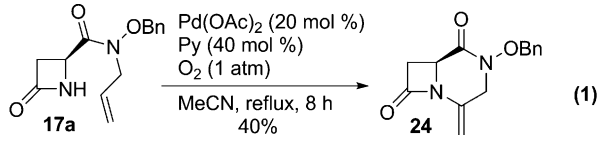
Scheme 4. Syntheses of (*S*)-4-*N*-[Allyl/Crotyl]-*N*-(benzyloxy)carboxamide β-Lactams 17a/17b



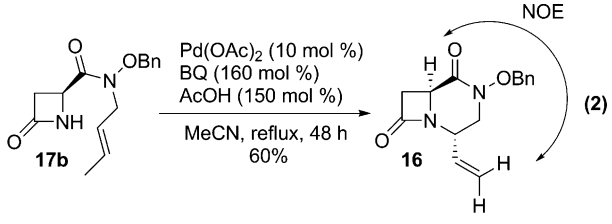
With pendant alkene-containing β-lactam **17a** in hand, we investigated cyclization conditions. We found that aza-Wacker cyclization conditions[21] gave the desired bicycle **24** in fair yield (eq 1). Attempts to optimize this reaction revealed that MeCN



(1)

was a superior solvent compared with either toluene or DMSO. Changing the catalyst loading failed to improve the yield. Molecular sieves were added in an attempt to alleviate the problem of catalyst aggregation[22] to no avail. Addition of Cs_2CO_3 resulted in polymerization of the starting material. Further functionalization of **24** was attempted; however, epoxidation,[23] aldehyde-selective Wacker oxidation,[24] hydroboration–oxidation,[25] and allylic oxidation with selenium[26] were not effective.

At this point, we hypothesized that the use of the crotyl-containing monocyclic β-lactam **17b** would provide access to a more readily functionalizable alkene-containing bicyclic β-lactam, **16** (eq 2). Aza-Wacker conditions from the synthesis



(2)

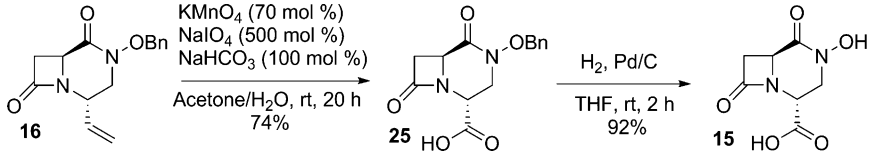
of **24** gave the desired product **16** as a single diastereomer in low yield (8%) after an extended reaction time (3 days). Switching to BQ as the oxidant in acetic acid (100 mol % BQ, 110 mol % AcOH)[27] increased the yield to 35%. Finally, increasing the loadings of BQ and AcOH to 150 and 160 mol %, respectively, gave **16** in 60% yield. The configuration shown in the structure of **16** was assigned by ROESY NMR. Formation of this single diastereomer was very exciting since it was anticipated that eventual conversion to carboxylic acid **25** would then give the relative and absolute configuration at the two stereogenic centers most often associated with biological activity of bicyclic β-lactams.

Oxidation of the pendent alkene **16** to the desired carboxylic acid **25** was achieved by ozonolysis followed by a Pinnick oxidation (Scheme 5). The best results were obtained using Lemieux–von Rudloff oxidation[28] conditions to give **25** in 74% yield. Hydrogenolysis then gave the final product **15** in 92% yield (Scheme 5).

Encouraged by these results, we were interested in seeing whether this approach would be compatible with syntheses of C-3-substituted β-lactam analogues. Here we describe results that include incorporation of a 3-hydroxyethyl side chain, peripheral functionalization that has been shown to be important for the activity of carbapenems as previously illustrated in **6**–**14**. Commercially available 3-hydroxyethyl-4-acetoxy-β-lactam **26** was allylated with In(s), NaI, and allylbromide to give **27** (Scheme 6).[29] Isomerization of the 4-allyl side chain with $RuHCOCl(PPh)_3$[30] gave 4-(2-propene)-substituted compound **28**, which was oxidized to 4-carboxylic acid **29**[31] with $KMnO_4/NaIO_4$. EDC·HCl coupling with *N*-crotyl-*O*-benzylhydroxylamine hydrochloride (**20b**) gave pendant-alkene-containing β-lactam **30** in fair yield. Treatment of **30** with the optimized conditions from the palladium-catalyzed cyclization of **16** gave bicyclic product **31** in good yield. Oxidation of the alkene with $KMnO_4/NaIO_4$ gave product **32** containing the carboxylic acid.

Although **15** does not have the α-amido side chain normally required for antibiotic activity, we screened it against a representative set of Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Mycobacterium vaccae*) and

Scheme 5. Elaboration to the Fully Functionalized Core (15)



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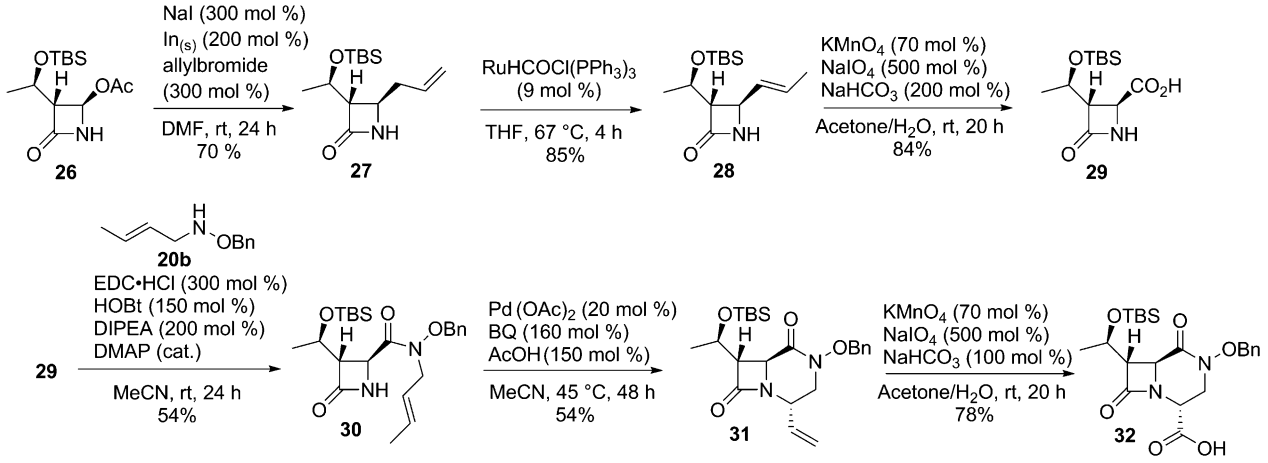
Scheme 6. Synthesis of C-3-Substituted Bicyclic β-Lactam 32



Gram-negative (*Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumannii*) bacteria. As expected, bicyclic β-lactam **15** was not active. Screening of **32** showed that it was also inactive. Future studies will focus on the incorporation of additional peripheral functionality. The methodology reported here should be of considerable general utility for the formation of bicyclic β-lactams.

■ CONCLUSIONS

We have demonstrated that Pd(II)-catalyzed oxidative amidation can be applied to highly functionalized β-lactams to diastereoselectively give a novel bicyclic core. This core can then be functionalized to give the carboxylic acid in one step. This methodology is compatible with a C-3 hydroxyethyl side chain common in carbapenems.

■ EXPERIMENTAL SECTION

General Methods. Reagents and solvents were purchased from commercial suppliers and used without purification, unless otherwise noted. 1,4-Benzoquinone was sublimed before use, and MeCN was distilled over CaH_2 for the EDC·HCl couplings. Chromatography was carried out on 230−400 mesh silica gel. NMR analysis was obtained at 25 °C on a 400, 500, or 600 MHz instrument. Chemical shifts are given in parts per million relative to residual solvent peaks. High-resolution mass spectrometry was conducted with electrospray ionization and a time-of-flight analyzer. Specific rotation ($[\alpha]_D$) was calculated using $(100{\cdot}\alpha)/(l{\cdot}c)$, where the concentration c was in units of g/100 mL.

(*S*)-*N*-Allyl-*N*-(benzyloxy)-4-oxoazetidine-2-carboxamide (17a). (*S*)-4-Oxoazetidine-2-carboxylic acid (**23**)[20] (0.77 g, 6.70 mmol), *N*-allyl-*O*-benzylhydroxylamine hydrochloride (**20a**)[18] (1.33 g, 6.70 mmol), and HOBt (1.36 g, 10.01 mmol) were suspended in freshly distilled MeCN. DIPEA (2.3 mL, 13.40 mmol) was added, followed by EDC·HCl (3.85 g, 20.10 mmol). After 16 h, the reaction mixture was concentrated under reduced pressure. The crude product was dissolved in DCM, extracted with 0.5 M citric acid, and then washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography with EtOAc/hexanes (3:1) gave **17a** as a pale-yellow oil (1.10 g, 62%). $[\alpha]_D$ = −79.6 (c = 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (dd, 1H, J = 14.9, 3.2 Hz), 3.12 (ddd, 1H, J = 14.9, 5.9, 1.6 Hz), 4.24 (dd, 1H, J = 5.5, 2.8 Hz), 4.29 (m, 2H), 4.84 (s, 2H), 5.29 (m, 2H, J = 15.3, 9.4, 1.2 Hz), 5.86 (m, 1H, J = 16.2, 10.3, 6.3 Hz), 6.08 (br s, 1H), 7.37 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 47.1, 49.6, 76.9, 119.6, 129.2, 129.5, 129.6, 131.6, 134.1, 166.8, 172.1; IR (Et_2O) ν 1667, 1768 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3$ 261.1234, found 261.1204.

(*S*)-*N*-(Benzyloxy)-*N*-(but-2-en-1-yl)-4-oxoazetidine-2-carboxamide (17b). (*S*)-4-Carboxy-2-azetidinone (**23**)[20] {$[\alpha]_D$ = −46.2 (c = 2.1, $CHCl_3$); lit.[20] −43.4 (c = 3.3, $CHCl_3$)} (0.99 g, 8.60 mmol), hydroxylamine hydrochloride **20b**[19] (1.83 g, 8.60 mmol), and HOBt (1.74 g, 12.90 mmol) were suspended in 66 mL of freshly distilled MeCN. Disopropylamine (3 mL, 17.20 mmol) was added, followed by EDC·HCl (4.90 g, 25.80 mmol). After 24 h, the mixture was concentrated under reduced pressure. The crude product was dissolved in DCM, extracted with 0.5 M citric acid, and then washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography with 3:1−4:1 EtOAc/hexanes gave **17b** as an amber oil (1.90 g, 81%). $[\alpha]_D$ = −85.0 (c = 3.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 3H), 2.97 (dd, 1H, J = 14.8, 2.9 Hz), 3.11 (ddd, 1H, J = 14.8, 5.5, 1.2 Hz), 4.21 (dd, 1H, J = 5.5, 2.9 Hz), 4.29 (m, 2H), 4.83 (s, 2H), 5.55 (m, 1H, J = 8.6, 6.7, 1.7 Hz), 5.75 (m, 1H, J = 8.6, 6.5, 1.2 Hz), 5.88 (br s, 1H), 7.37 (m, 5H) [the crotyl bromide used in the synthesis of **20b** was 85% trans; cis isomer 4.85 (s)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 43.1, 47.2, 48.8, 77.0, 124.3, 129.1, 129.5, 129.6, 131.3, 134.2, 167.0, 171.9 [cis isomer 13.3, 123.6]; IR (Et_2O) ν 1666, 1767 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3$ 275.1390, found 275.1374.

(*S*)-4-(Benzyloxy)-2-methylene-1,4-diazabicyclo[4.2.0]-octane-5,8-dione (24). $Pd(OAc)_2$ (0.03 g, 0.14 mmol) and pyridine (0.03 mL, 0.28 mmol) were suspended in 8 mL of MeCN. O_2 was bubbled through the solution for 10 min. The lemon-yellow solution was then heated in an oil bath at 73 °C for 10 min under 1 atm O_2. A solution of (*S*)-*N*-allyl-*N*-(benzyloxy)-4-oxoazetidine-2-carboxamide (**17a**) (0.18 g, 0.69 mmol) in 9 mL of MeCN was added. After 8 h, the mixture was concentrated under reduced pressure. Chromatography of the residue with EtOAc/hexanes (2:1) gave **24** as an off-white solid (0.07 g, 40%). Mp 83−86 °C; $[\alpha]_D$ = −60.5 (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (m, 2H, J = 15.7, 5.1, 3.5 Hz), 3.76 (d, 1H, J = 14.8 Hz), 4.18 (dd, 1H, J = 5.1, 3.5 Hz), 4.23 (dt, 1H, J = 14.9, 1.8 Hz), 4.32 (m, 1H), 5.0 (m, 2H), 5.01 (t, 1H, J = 1.6 Hz) 7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 49.8, 54.0, 76.9, 96.5, 129.0, 129.5, 130.0, 134.1, 134.7, 165.0, 166.1; IR (Et_2O) ν 1689, 1771 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{14}H_{14}N_2O_3$ 259.1077, found 259.1099.

(2*S*,6*S*)-4-(Benzyloxy)-2-vinyl-1,4-diazabicyclo[4.2.0]octane-5,8-dione (16). $Pd(OAc)_2$ (0.04 g, 0.17 mmol), 1,4-benzoquinone (0.30 g, 2.75 mmol), and acetic acid (0.15 mL, 2.58 mmol) were dissolved in 10 mL of MeCN. A solution of (*S*)-*N*-(benzyloxy)-*N*-(but-2-en-1-yl)-4-oxoazetidine-2-carboxamide (**17b**) (0.47 g, 1.72 mmol) in 7 mL of MeCN was added, and the bright-orange solution was heated at 70 °C under air. After 49 h, the reddish-brown suspension was concentrated under reduced pressure to give a gummy black solid, which was suspended in DCM and filtered to remove the catalyst and hydroquinone. Chromatography with a gradient of pure DCM to 1:1 DCM/ether to ether gave the desired product **16** as an amber oil (0.28 g, 60% yield). $[\alpha]_D$ = −42.6 (c = 0.8, CH_2Cl_2); ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 3.15 (dd, 1H, J = 15.7, 2.5 Hz), 3.38 (dd, 1H, J = 12.5, 5.6 Hz), 3.42 (dd, 1H, J = 15.7, 5.9 Hz), 3.68 (dd, 1H, J = 12.5, 5.6 Hz), 4.08 (dd, 1H, J = 5.9, 2.5 Hz), 4.29 (m, 1H, J = 10.3, 5.7, 1.4 Hz), 5.05 (m, 2H), 5.24 (m, 2H, J = 17.0, 10.1, 3.1, 1.2 Hz), 5.48 (ddd, 1H, J = 17.0, 10.1, 4.5 Hz), 7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 49.0, 51.9, 54.6, 76.9, 118.7, 129.0, 129.5, 130.1, 132.6, 134.9, 166.8, 169.4; IR (Et_2O) ν 1685, 1763 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{16}N_2NaO_3$ 295.1053, found 295.1028.

(2*R*,6*S*)-4-(Benzyloxy)-5,8-dioxo-1,4-diazabicyclo[4.2.0]-octane-2-carboxylic Acid (25). Bicyclic alkene **16** (0.26 g, 0.94 mmol) was dissolved in acetone/water (18 mL/10 mL). The pale-brown solution was purged with Ar, and then $KMnO_4$ (0.10 g, 0.66 mmol), $NaIO_4$ (1.01 g, 4.70 mmol), and $NaHCO_3$ (0.08 g, 0.94 mmol) were added. After 19 h, the pH was adjusted to 2 with 2 M HCl, and the solution was filtered through Celite with EtOAc. The biphasic solution was extracted with EtOAc. The organic fractions were extracted with 0.1 M Na_2SO_3. The aqueous fractions were adjusted to pH 2 with 3 M HCl and extracted with EtOAc. The organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the desired product **25** as an off-white foam (0.20 g, 74%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.09 (dd, 1H, J = 15.5, 2.6 Hz), 3.45 (dd, 1H, J = 15.5, 5.7 Hz), 3.91 (dd, 1H, J = 12.2, 4.7 Hz), 4.00 (dd, 1H, J = 12.6, 6.3 Hz), 4.26 (dd, 1H, J = 5.9, 2.4 Hz), 4.62 (dd, 1H, J = 6.3, 4.3 Hz), 4.95 (m, 2H), 7.41 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 49.4, 51.3, 52.1, 76.9, 129.0, 129.6, 130.0, 134.4, 167.0, 169.1, 170.0; IR (Et_2O) ν 1679, 1749 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{14}N_2NaO_5$ 313.0795, found 313.0786.

(2*R*,6*S*)-4-Hydroxy-5,8-dioxo-1,4-diazabicyclo[4.2.0]octane-2-carboxylic Acid (15). Bicyclic carboxylic acid **25** (0.20 g, 0.69 mmol) was dissolved in 8 mL of peroxide-free THF. The pale-yellow solution was purged with Ar. Pd/C (10% Pd, 0.02 g, 0.02 mmol of Pd) was added, and the black suspension was degassed under vacuum. The reaction flask was purged with hydrogen, and the hydrogen atmosphere was maintained with a hydrogen balloon. After 2 h, the suspension was purged with Ar, filtered through glass filter paper with MeOH, and concentrated to give **15** as a white foam (0.13 g, 92%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.11 (dd, 1H, J = 15.4, 2.5 Hz), 3.49 (dd, 1H, J = 15.4, 5.9 Hz), 4.00 (dd, 1H, J = 12.7, 3.1 Hz), 4.17 (dd, 1H, J = 12.4, 6.2 Hz), 4.29 (dd, 1H, J = 6.0, 2.4 Hz), 4.86 (dd, 1H, J = 6.1, 3.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 42.1, 48.5, 51.0, 52.8, 166.3, 169.5, 169.8; IR (Et_2O) ν 1654, 1747 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_7H_7N_2O_5$ 199.0360, found 199.0340.

(3*S*,4*R*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(prop-1-en-1-yl)azetidin-2-one (28). (3*S*,4*R*)-4-Allyl-3-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)azetidin-2-one (**27**) (0.20 g, 0.74 mmol) was dissolved in 7 mL of freshly distilled THF, and the suspension was purged with Ar for 10 min. $RuHCOCl(PPh_3)_3$ (0.06 g, 0.07 mmol) was added, and the reaction mixture was heated in an oil bath at 76 °C. After 4 h, the solution was concentrated under vacuum and chromatographed on silica gel with 2:1 hexanes/EtOAc to give a waxy brown solid (0.17 g, 85%). $[\alpha]_D$ = −14.1 (c = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 1.20 (d, 3H, J = 6.3 Hz), 1.71 (d, 3H, J = 6.7 Hz), 2.84 (m, 1H, J = 2.7, 1.9, 0.9 Hz), 4.14 (d, 1H, J = 7.5 Hz), 4.21 (qd, 1H, J = 6.3, 4.7 Hz), 5.55 (m, 1H, J = 7.8, 1.2 Hz), 5.73 (m, 1H, J = 14.6, 6.3 Hz), 5.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.0, 13.5, 17.8, 18.2, 22.6, 25.9, 39.7, 46.2, 50.4, 52.1, 64.0, 64.9, 65.6, 65.7, 65.9, 66.3, 118.2, 128.2, 128.5, 130.3, 130.9, 168.9 [mix of cis (minor) and trans (major) isomers]; IR (Et_2O) ν 1642 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{28}NO_2Si$ 270.1884, found 270.1881.

(2*S*,3*S*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-oxoazetidine-2-carboxylic acid (29). (3*S*,4*R*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(prop-1-en-1-yl)azetidin-2-one (**28**) (0.09 g, 0.33 mmol) was dissolved in acetone/water (6 mL/2 mL). Potassium permanganate (0.04 g, 0.23 mmol), sodium periodate (0.35 g, 1.66 mmol), and sodium bicarbonate (0.06 g, 0.66 mmol) were added in one portion. After 19 h, the mixture was treated with $NaHSO_3$ until the purple suspension became clear yellow. The aqueous solution was extracted with EtOAc (×4). The combined organic fractions were extracted with $NaHSO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give an oily yellow solid (0.08 g, 84%). $[\alpha]_D$ = −13.0 (c = 0.3, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (d, 6H, J = 6.6 Hz), 0.88 (s, 9H), 1.26 (d, 3H, J = 6.4 Hz), 3.36 (td, 1H, J = 2.7, 1.2 Hz), 4.32 (ddd, 1H, J = 12.5, 6.4, 2.7 Hz), 4.38 (dd, 1H, J = 2.2, 0.5 Hz), 6.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −4.1, 18.2, 22.5, 25.9, 29.9, 49.3, 64.2, 64.9, 169.4, 175.6; IR (Et_2O) ν 1643, 1751 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{12}H_{22}NO_4Si$ 272.1324, found 272.1325.

(2*S*,3*S*)-*N*-(Benzyloxy)-*N*-(but-2-en-1-yl)-3-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-oxoazetidine-2-carboxamide (30). *N*-Crotyl-*O*-benzylhydroxylamine hydrochloride (**20b**) (0.16 g, 0.73 mmol), HOBt (0.15 g, 1.10 mmol), cat. DMAP, and carboxylic acid **29** (0.20 g, 0.73 mmol) were suspended in 10 mL of freshly distilled MeCN under Ar. Hunig's base (0.25 mL, 1.46 mmol) was added, followed by EDC·HCl (0.42 g, 2.20 mmol). After 24 h, the mixture was concentrated under vacuum; diluted with DCM; extracted with 0.5 M citric acid (×2), 4% $NaHCO_3$ (×2), water, and brine; dried over $MgSO_4$; filtered; and reduced to give an amber oil. Column chromatography on silica gel with 1:1 hexanes/EtOAc gave a waxy pale-amber solid (0.17 g, 54%). $[\alpha]_D$ = −1.4 (c = 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.11 (d, 3H, J = 6.3 Hz), 1.72 (dd, 3H, J = 6.3, 1.6 Hz), 3.34 (td, 1H, J = 2.4, 1.2 Hz), 4.15−4.35 (m, 3H), 4.39 (dd, 1H, J = 5.5, 2.4 Hz), 4.86 (s, 2H), 5.51 (m, 1H, J = 12.6, 6.3, 1.6 Hz), 5.62 (br s, 1H), 5.75 (ddd, 1H, J = 13.0, 6.3, 1.2 Hz), 7.31−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.1, 13.3, 18.0, 18.2, 22.5, 26.0, 43.4, 48.2, 48.3, 48.6, 63.6, 64.2, 76.9, 123.8, 124.5, 129.0, 129.3, 129.5, 129.6, 131.0, 133.9, 168.5, 171.7 [mix of cis (minor) and trans (major) isomers]; IR (Et_2O) ν 1653, 1749 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{37}N_2O_4Si$ 433.2517, found 433.2534.

(6*S*,7*S*)-4-Benzyloxy-7-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-ethyl)-2-vinyl-1,4-diazabicyclo[4.2.0]octane-5,8-dione (31). Palladium acetate (0.02 g, 0.07 mmol), benzoquinone (0.06 g, 0.52 mmol), and acetic acid (0.03 mL, 0.49 mmol) were dissolved in 1 mL of MeCN. (2*S*,3*S*)-*N*-(Benzyloxy)-*N*-(but-2-en-1-yl)-3-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-oxoazetidine-2-carboxamide (**30**) (0.14 g, 0.33 mmol) in 3 mL of MeCN was added. The flask containing the solution was placed in an oil bath at 45 °C. After 48 h, the reaction mixture was concentrated under vacuum; diluted with DCM; extracted with 10% $NaHSO_3$ (×3), 4% $NaHCO_3$ (×3), and brine; dried over $MgSO_4$; filtered; and concentrated to give a pale-tan oil. Chromatography with 2:1 hexanes/EtOAc gave a pale-yellow oil (0.08 g, 54%). $[\alpha]_D$ = −36.3 (c = 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.28 (d, 3H, J = 6.4 Hz), 3.33 (t, 1H, J = 2.5 Hz), 3.37 (dd, 1H, J = 12.2, 4.9 Hz), 3.71 (dd, 1H, J = 12.2, 5.6 Hz), 4.20 (d, 1H, J = 2.7 Hz), 4.30−4.37 (m, 2H), 4.95−5.02 (m, 2H), 5.21 (dq, 1H, J = 10.3, 1.0 Hz), 5.28 (dq, 1H, J = 17.1, 1.0 Hz), 5.46 (ddd, 1H, J = 17.1, 10.3, 4.7 Hz), 7.35−7.45 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.4, 18.2, 22.7, 25.9, 26.0, 29.9, 50.3, 51.3, 54.8, 63.8, 64.0, 76.9, 118.6, 128.9, 129.4, 130.1, 132.8, 135.0, 167.3, 169.7; IR (Et_2O) ν 1683, 1766 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{35}N_2O_4Si$ 431.2361, found 431.2352.

(6*S*,7*S*)-4-(Benzyloxy)-7-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-ethyl)-5,8-dioxo-1,4-diazabicyclo[4.2.0]octane-2-carboxylic acid (32). (6*S*,7*S*)-4-(Benzyloxy)-7-((*R*)-1-((*tert*-butyldimethylsilyl)-oxy)ethyl)-2-vinyl-1,4-diazabicyclo[4.2.0]octane-5,8-dione (**18**) (0.04 g, 0.09 mmol) was dissolved in acetone/water (3 mL/1 mL), and the solution was purged with Ar for 10 min. Potassium permanganate (0.01 g, 0.07 mmol), sodium periodate (0.10 g, 0.47 mmol), and sodium bicarbonate (0.01 g, 0.09 mmol) were added in one portion. After 17 h, the reaction was quenched with 10% $NaHSO_3$, and the mixture was extracted with EtOAc (×3). The combined organic fractions were washed with 10% $NaHSO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to give a clear glass (0.03 g, 78%). $[\alpha]_D$ = −7.6 (c = 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 1.28 (d, 3H, J = 6.4 Hz), 3.39 (d, 1H, J = 5.1 Hz), 3.78 (dd, 1H, J = 12.2, 3.9 Hz), 3.88 (dd, 1H, J = 12.2, 6.1 Hz), 4.32 (qd, 1H, J = 6.2, 2.2 Hz), 4.41 (d, 1H, J = 2.7 Hz), 4.54

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(dd, 1H, J = 6.1, 3.9 Hz), 4.90−5.02 (m, 2H), 7.34−7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −4.2, 18.1, 22.6, 25.8, 25.9, 29.9, 50.8, 50.9, 52.5, 63.7, 65.0, 77.0, 129.0, 129.5, 130.0, 131.1, 134.6, 167.1, 169.4, 171.4; IR (Et_2O) ν 1652, 1749 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{22}H_{31}N_2O_6Si$ 447.1957, found 447.1924.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mmiller1@nd.edu.

Notes

The authors declare no competing financial interest.

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