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Stereocontrolled Formation of a [4.4]Heterospiro Ring System with Unexpected Inversion of Configuration at the Spirocenter

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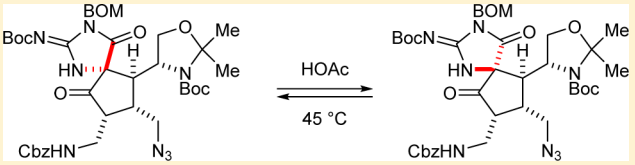
Supporting Information

ABSTRACT: Stereoselective construction of the 1,3-diazaspiro[4.4]nonane core skeleton of massadine and related dimeric pyrrole−imidazole alkaloids is a synthetic challenge. We describe herein the synthesis of all C13/14 diastereomers of this spiro molecule through controlled oxidation and epimerization of the C13 spirocenter under mild acidic conditions.



The complex molecular skeleton of massadine (**1**)[1] (Figure 1) and related pyrrole−imidazole alkaloids has provided chemists with a unique platform for studying the reactivity of highly nitrogenated small molecules.[2−6] Among all synthetic challenges associated with **1**, stereoselective construction of the fully functionalized, cyclic guanidine-containing spirocyclic skeleton is arguably the most important task. One popular strategy involves oxidative rearrangement of dibromoageliferin (**2**)[7] or its analogues.[8−11] This approach originates from Scheuer's biosynthetic hypothesis that palau'amine was produced from **3** through oxidative ring contraction.[12] Later, it was found that the structure of palau'amine was initially misassigned, and the then believed structure of palau'amine is 12,17,20-*epi*-palau'amine (**4**).[13] Additionally, we have recently discovered that the absolute stereochemistry of **2** was also misassigned, and **2** is antipodal to **1**.[3] Although these findings disprove the biogenic role of the "Scheuer rearrangement", this oxidative rearrangement reaction continues to play an important role in synthetic chemistry. We report herein the stereoselective formation of the core structure of **1** using Scheuer rearrangement and an unexpected epimerization of the C13 spirocenter under mild acidic conditions.

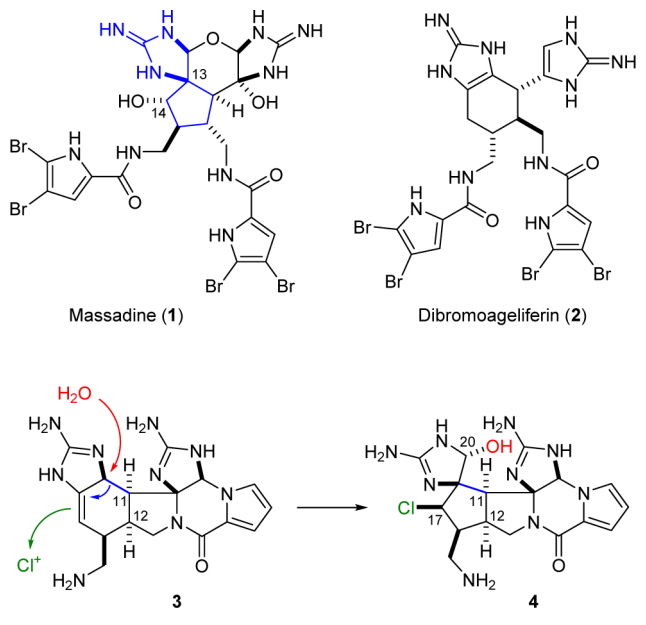


Figure 1. Structures of massadine (**1**) and dibromoageliferin (**2**) and the Scheuer rearrangement of **3** to produce palau'amine (**4**).

Our study of the Scheuer rearrangement started with oxidation of **5** with dimethyldioxirane (DMDO) (Figure 2). NMR analyses of the product indicated that DMDO approached **5** from its less-hindered β-face to give epoxide **6**.[8c] Subsequent epoxide-opening provided zwitterion **7** that underwent a semipinacol-type rearrangement to yield **8** with the undesired spiro configuration (path a). The alternative path b would lead to the formation of **10** through **9** with the same spiro configuration but a different position of the benzyloxymethyl (BOM) group. We note that it is also likely that the oxidation of **5** gave **7** or its isopropylidene acetal directly without the intermediacy of **6**.

To establish the desired spiro configuration, we explored the possibility of using the hydroxyl group of **5** to direct the oxidant to approach from its more hindered α-face (Figure 3). Initial attempts using vanadyl acetylacetonate mediated epoxidation indeed led to the formation of a rearrangement product that is diastereomeric to **8**. However, NMR studies indicated that it also bears the undesired C13 spiro configuration, suggesting that the oxidant still approached from the less hindered β-face of **5**. Surprisingly, the C14 stereocenter was epimerized during the oxidation to give **11**.

We next found that switching the oxidant to titanium tetraisopropoxide led to the formation of another diastereomer of **8**. NMR analyses of this oxidation product of **5** indicated the formation of **12** with the correct C13 spiro configuration. The

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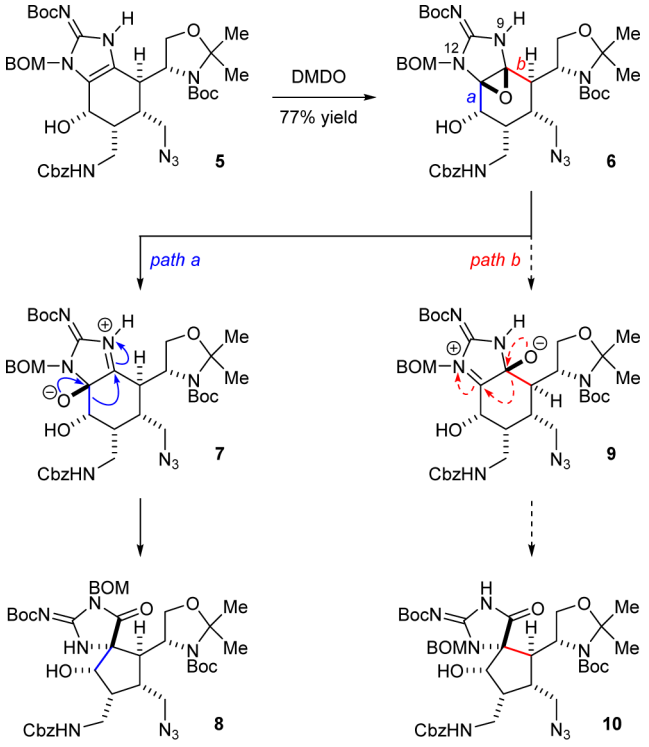

Figure 2. Two possible rearrangement pathways for the oxidative ring-contraction of **5**.

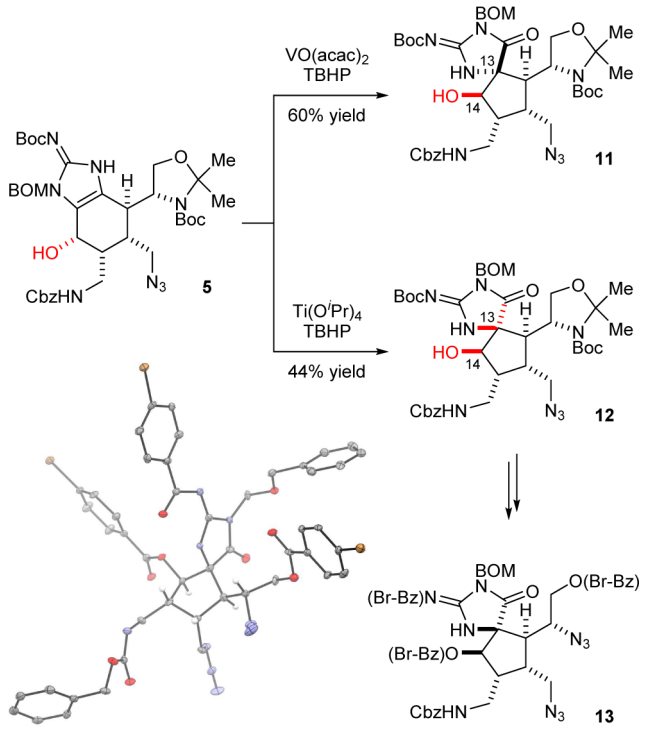

Figure 3. Epimerization of the C14 stereocenter during the oxidation of **5** (thermal ellipsoids of **13** shown at a 30% probability level).

structure of **12** was later confirmed by X-ray analysis of its crystalline derivative **13**. The titanium oxidant likely approached from the more hindered α-face through coordination to the C14 hydroxyl group of **5** in this oxidation reaction. However, the C14 stereocenter was also epimerized. Addition of (+)- or (−)-diethyl tartrate had no effects on the stereochemical outcomes of this reaction. We further prepared the fourth C13/C14 diastereomer **14** by inversion of the C13 stereocenter of **12** through alcohol oxidation/ketone reduction (Figure 4). With all four possible diastereomers in hand, a

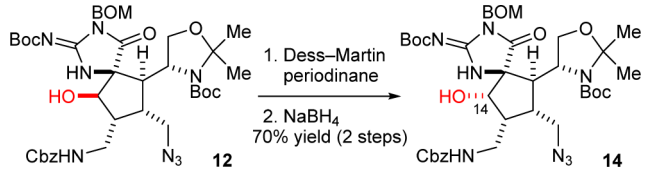

Figure 4. Preparation of **14** by oxidation/reduction of **12**.

comparison of the NOE data of **8**, **11**, **12**, and **14** provided strong support to the depicted relative stereochemistry of these compounds.

To better understand the reaction pathway that led to the isomerization of the C14 stereocenter of **11** and **12**, we carried out the following control experiments. We first exposed α-alcohol **5** to vanadyl acetylacetonate and titanium tetraisopropoxide independently but did not find the formation of β-alcohol **15** (Figure 5). Therefore, it is less likely that C14 isomerization

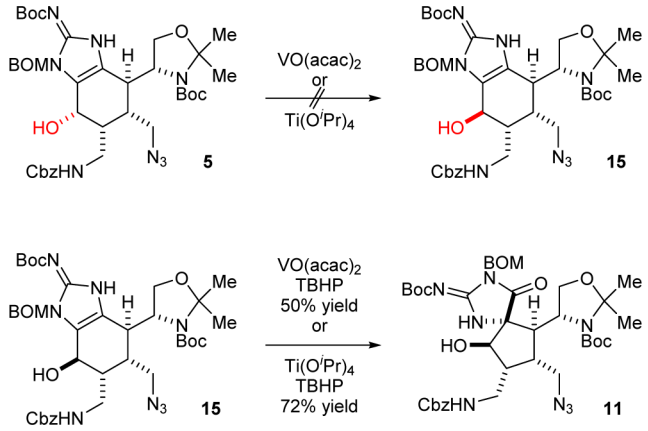

Figure 5. C14 stereocenter did not isomerize in the presence of vanadyl acetylacetonate or titanium tetraisopropoxide. Vanadium- and titanium-mediated oxidation of **15** gave the same product **11**.

occurred before epoxidation. We next compared the oxidation of **5** and **15** and found that vanadium-mediated oxidation of α-alcohol **5** and β-alcohol **15** both gave **11**, whereas the titanium-mediated oxidations of **5** and **15** gave **12** and **11**, respectively. These results indicate that the stereoselectivity of the vanadium-mediated oxidation was determined by the steric environment of **5**. In contrast, the titanium-mediated oxidation is controlled by the C14 configuration potentially due to a stronger metal−oxygen interaction. Collectively, C14-epimerization likely occurred after oxidative ring-contraction. The vanadium-mediated oxidation of **5** gave **11** through **8**, and the titanium-mediated oxidation of **5** gave **12** through **14**.

Although we have not been able to directly convert **8** to **11** or **14** to **12** under a variety of conditions, the following experiments suggested that epimerization of the C14 stereocenter occurred through cleavage of the C13−C14 linkage. Dess−Martin oxidation of **11** and **12** gave ketones **16** and **17**, respectively (Figure 6). Treatment of **16** with acetic acid at 45 °C provided a 1:1 mixture of **16** and **17**. We believe that this isomerization occurred through reversible Claisen condensation and is mechanistically similar to the C13 epimerization reaction

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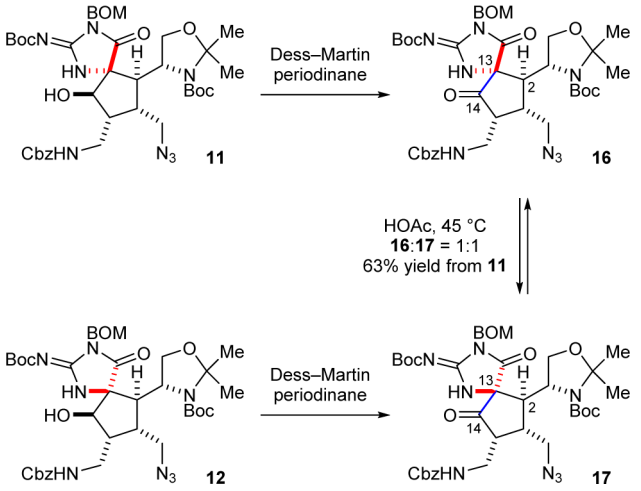

Figure 6. Equilibrium of the C13 quaternary stereocenter.

reported by Harran wherein the C2−C13 linkage was cleaved upon thermolysis.[7e]

In summary, Scheuer rearrangement allows for easy access to the spiro core skeleton of massadine (**1**) from stereochemically simple starting materials. In the presence of a C14 hydroxyl group, this oxidative ring-contraction reaction can proceed with stereochemical control to give a diverse set of C13/14 diastereomers under different reaction conditions. Additionally, the C13 quaternary spirocenter can be epimerized under mild acidic conditions in the presence of a C14 hydroxyl or ketone group.

EXPERIMENTAL SECTION

All reactions were performed in glassware under a positive pressure of argon. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in ppm (δ) relative to the residual ^{1}H and ^{13}C signals of the solvent ($CDCl_3$: δ 7.26, 77.16 ppm; DMSO-d_6: δ 2.50, 39.52 ppm; CD_3CN: δ 1.94, 1.32, 118.26 ppm; benzene-d_6: δ 7.16, 128.06 ppm) and the multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

(4*S*,5*R*,6*S*,7*R*)-6-Azidomethyl-3-(benzyloxymethyl)-5-((((benzyloxy)carbonyl)amino)methyl)-2-(*tert*-butoxycarbonylimino)-7-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2,3,4,5,6,7-hexahydro-1*H*-benz[*d*]imidazol-4-ol (5) and (4*R*,5*R*,6*S*,7*R*)-6-(Azidomethyl)-3-(benzyloxymethyl)-5-((((benzyloxy)carbonyl)amino)methyl)-2-(*tert*-butoxycarbonylimino)-7-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2,3,4,5,6,7-hexahydro-1*H*-benz[*d*]imidazol-4-ol (15). To a solution of (*E*)-3-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)allyl 3-(((benzyloxy)carbonyl)amino)propanoate[11b] (11.9 g, 25.7 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (320 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (69.9 mL, 1.0 M in tetrahydrofuran, 69.9 mmol, 3.0 equiv) dropwise. After the mixyure was stirred at −78 °C for 0.5 h, a solution of 2-azido-1-((benzyloxy)methyl)-1*H*-imidazole-5-carbaldehyde[7c] (6.0 g, 23.3 mmol, 1.0 equiv) in tetrahydrofuran (50 mL) was added through a stainless steel cannula over 10 min. The reaction was then stirred at −78 °C for 2 h before being quenched with an acetic acid solution in tetrahydrofuran (1:4 v/v, 20 mL). After the solvent was removed by rotary evaporator, the residue was dissolved in ethyl acetate, washed with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated. The resulting crude aldol product was then dissolved in anhydrous methylene chloride (630 mL), and Dess−Martin periodinane (19.8 g, 46.6 mmol, 2.0 equiv) was added at 23 °C followed by water (0.63 mL, 35.0 mmol, 1.3 equiv). After the white suspension was stirred for 2 h, the reaction was quenched with a mixture of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v) and stirred for another 10 min. After the solvent was removed by rotary evaporator, the suspension was then extracted with ethyl acetate, and the organic phase was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. Subsequently, to a 1 L round-bottom flask charged with the resulting crude β-ketoester and manganese(III) acetate dihydrate (18.2 g, 67.9 mmol, 2.9 equiv) was added acetic acid (305 mL) followed by degassing with three freeze−pump−thaw cycles. After the mixture was stirred at 50 °C for 15 h, acetic acid was removed, and the residue was dissolved in ethyl acetate, washed successively with 10% aqueous sodium bisulfite solution and brine, dried over sodium sulfate, filtered, and concentrated. The resulting crude lactone product was dissolved in tetrahydrofuran (900 mL), and lithium hydroxide (440 mL, 149.6 mmol, 6.4 equiv, 0.34 N in water) was added 23 °C. After the mixture was stirred for 2 h, the solvents were removed by rotary evaporation, and the residue was partitioned between ethyl acetate and brine. The organic layer was separated and washed successively with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated. To the resulting crude alcohol (14 g, 20.3 mmol, 1 equiv) in anhydrous methylene chloride (200 mL) was added triethylamine (8.5 mL, 60.9 mmol, 3.0 equiv) followed by methanesulfonyl chloride (3.2 mL, 40.6 mmol, 2.0 equiv) at 5 °C. The mixture was warmed to 23 °C and stirred for 1 h, the solvent was removed, and the residue was dissolved in ethyl acetate, washed with aqueous hydrogen chloride (0.1 N), saturated aqueous sodium bicarbonate, and brine, dried over sodium sulfate, filtered, and concentrated. The resulting crude mesylate was dissolved in acetone (550 mL), and sodium iodide (92.0 g, 614 mmol, 30.2 equiv) was added. After the mixtre was stirred at 70 °C for 5 h, the solvent was removed, and the residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was further washed with an aqueous solution of 10% sodium thiosulfate and brine, dried over sodium sulfate, filtered, and concentrated. The resulting crude iodide was dissolved in anhydrous dimethyl sulfoxide (55 mL), and sodium azide (6.6 g, 102 mmol, 5.0 equiv) was added. After being stirred at 60 °C for 3 h, the reaction mixture was partitioned between ethyl acetate and brine, and the organic layer was further dried over sodium sulfate, filtered, concentrated, and purified by a Biotage KP-C18-HS column (71 × 168 mm, 340 g) (55% → 75% acetonitrile/water) to give (5*R*,6*S*,7*R*)-2-azido-6-(azidomethyl)-3-(benzyloxymethyl)-7-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-5-((((benzyloxy)carbonyl)amino)methyl)-3,5,6,7-tetrahydro-4*H*-benzo[*d*]imidazol-4-one as a pale yellow solid (2.42 g, 15% yield over seven steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.16 (m, 10H), 5.63 (d, J = 10.5 Hz, 1H), 5.58−5.50 (m, 1H), 5.45 (d, J = 10.5 Hz, 1H), 5.12 (d, J = 12.1 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 4.70 (d, J = 9.1 Hz, 1H), 4.63 (s, 2H), 4.03 (dd, J = 10.7, 4.7 Hz, 1H), 3.79 (dd, J = 9.1, 4.9 Hz, 1H), 3.77−3.67 (m, 1H), 3.67−3.57 (m, 1H), 3.57−3.45 (m, 2H), 3.23 (dd, J = 10.7, 1.4 Hz, 1H), 2.86 (dd, J = 11.6, 11.6 Hz, 1H), 2.51−2.38 (m, 1H), 1.64 (s, 3H), 1.57 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 156.8, 154.4, 151.9, 147.5, 137.4, 136.7, 128.5, 128.4, 128.1, 128.0, 127.3, 124.0, 94.5, 81.5, 73.2, 72.1, 66.9, 65.6, 58.1, 49.5, 44.8, 41.2, 38.9, 37.7, 28.5, 27.9, 24.7; MS (ESI) m/z $[M + H]^+$ calcd for $C_{35}H_{43}N_{10}O_7$ 715.3, found 715.3. To a solution of the azide (600 mg, 0.84 mmol, 1.0 equiv) obtained above in methanol (14 mL) was added triethylamine (0.35 mL, 2.51 mmol, 3.0 equiv) followed by 1,3-propanedithiol (0.084 mL, 0.837 mmol, 1.0 equiv) at 0 °C. After being stirred at 23 °C for 16 h, the reaction mixture was filtered, and the volatiles were removed by rotary evaporation. The resulting residue was dissolved in ethyl acetate, washed successively with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated. To a solution of the crude aminoimidazole obtained above in methylene chloride (30 mL) and triethylamine (0.585 mL, 4.20 mmol, 5.0 equiv) were added di-*tert*-butyl dicarbonate (0.482 mL, 2.10 mmol, 2.5 equiv) and 4-(dimethylamino)pyridine (21.0 mg, 0.170 mmol, 0.2 equiv) at 23 °C. After the mixture was stirred at 23 °C for 4 h, the volatiles were removed by rotary evaporation, and the resulting residue was dissolved in ethyl acetate, washed successively with hydrochloric acid (0.1 N), saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered, and concentrated. To a solution of the crude bis-Boc-

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aminoimidazole (230 mg, 0.259 mmol, 1.0 equiv) obtained above in tetrahydrofuran (15 mL) was added lithium triethylborohydride (1.0 M in tetrahydrofuran, 3.1 mL, 3.1 mmol, 12.0 equiv) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was cooled to −60 °C and quenched with saturated ammonium chloride. The volatiles were then removed by rotary evaporation, and the resulting residue was dissolved with ethyl acetate, washed with brine, dried over sodium sulfate, filtered, concentrated, and purified by HPLC (Atlantis dC18 OBD, 19 × 150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 65% B, T = 30 min: 85% B, 5.0 mL/min; retention time: 21.8 min for **15** and 23.8 min for **5**) to give **5** as a pale yellow oil (74.0 mg, 36% yield over three steps) and **15** as a pale yellow oil (31.3 mg, 15% yield over three steps).

5: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.41−7.21 (m, 10H), 6.87 (t, J = 5.0 Hz, 1H), 5.34 (d, J = 10.9 Hz, 1H), 5.31 (d, J = 5.6 Hz, 1H), 5.17 (d, J = 11.0 Hz, 1H), 5.03 (s, 2H), 4.80 (d, J = 8.0 Hz, 1H), 4.72−4.65 (m, 1H), 4.44 (s, 2H), 3.81−3.70 (m, 2H), 3.66 (dd, J = 13.0, 3.1 Hz, 1H), 3.37−3.30 (m, 1H), 3.29−3.19 (m, 1H), 2.92 (dd, J = 12.1, 12.1 Hz, 1H), 2.82 (d, J = 10.2 Hz, 1H), 2.50−2.41 (m, 1H), 2.04 (d, J = 11.4 Hz, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4, 153.9, 153.2, 150.2, 139.1, 137.9, 137.4, 137.0, 132.8, 93.2, 79.9, 79.7, 71.9, 69.7, 65.5, 65.0, 59.0, 58.6, 50.9, 40.4, 39.9, 37.6, 35.4, 28.0, 27.9, 27.4, 24.5; MS (ESI) m/z [M + H]$^+$ calcd for $C_{40}H_{55}N_8O_9$ 791.4, found 791.3. **15**: ^{1}H NMR (400 MHz, CD_3CN) 7.43−7.12 (m, 10H), 6.20−6.05 (m, 1H), 5.52 (d, J = 10.8 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 1.8 Hz, 2H), 4.88−4.74 (m, 1H), 4.57−4.29 (m, 3H), 4.09−3.93 (m, 1H), 3.86−3.73 (m, 1H), 3.69−3.39 (m, 2H), 3.34−3.16 (m, 1H), 2.86−2.73 (m, 1H), 2.72−2.56 (m, 1H), 2.53−2.38 (m, 1H), 2.30−2.11 (m, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.43 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ 157.7, 155.2, 154.8, 150.9, 140.3, 138.5, 138.2, 134.8, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 94.8, 81.7, 81.6, 74.2, 71.2, 66.9, 66.0, 64.7, 60.2, 50.3, 42.3, 41.6, 40.8, 37.8, 28.6, 28.3, 27.9, 24.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{40}H_{55}N_8O_9$ 791.4087, found 791.4107.

(5*R*,6*R*,7*S*,8*R*,9*S*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-hydroxy-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (8). To a solution of **5** (26.0 mg, 0.033 mmol, 1.0 equiv) obtained above in acetone (0.70 mL) was added dimethyldioxirane (0.1 M in acetone, 0.73 mL, 0.073 mmol, 2.2 equiv) at 0 °C. After the mixture was stirred at 0 °C for 16 h, the volatiles were removed in vacuo (0.1 mmHg) at 0 °C, and the resulting residue was purified by HPLC (Atlantis dC18 OBD, 19 × 150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 30 min: 85% B, 5.0 mL/min; retention time: 25.9 min) to give **8** as a colorless oil (20.0 mg, 75% yield): ^{1}H NMR (600 MHz, DMSO-d_6, 45 °C) δ 8.77 (s, 1H), 7.39−7.22 (m, 10H), 7.18 (brs, 1H), 5.81 (brs, 1H), 5.04 (d, J = 12.7 Hz, 1H), 5.00 (d, J = 12.7 Hz, 1H), 4.95 (s, 2H), 4.59 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.33−4.20 (m, 1H), 3.81 (dd, J = 5.5, 3.6 Hz, 1H), 3.71−3.62 (m, 2H), 3.55−3.42 (m, 2H), 3.28−3.19 (m, 2H), 2.82−2.73 (m, 1H), 2.71 (dd, J = 9.4, 5.4 Hz, 1H), 2.60−2.51 (m, 1H), 1.49 (s, 3H), 1.45 (s, 9H), 1.43 (s, 9H), 1.36 (s, 3H); ^{1}H NMR (600 MHz, CD_3CN, 45 °C) δ 8.54 (s, 1H), 7.38−7.27(m, 10H), 5.82 (s, 1H), 5.09 (d, J = 12.5 Hz, 1H), 5.06 (d, J = 12.5 Hz, 1H), 4.99 (d, J = 1.6 Hz, 2H), 4.64 (d, J = 12.1 Hz, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.53−4.45 (m, 1H), 4.33−4.24 (m, 1H), 3.73−3.50 (m, 5H), 3.47−3.37 (m, 1H), 3.36−3.28 (m, 1H), 2.88−2.76 (m, 1H), 2.75−2.63 (m, 2H), 1.51 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 174.1, 163.63, 163.59, 160.2, 158.5, 138.9, 138.1, 129.4, 129.3, 128.9, 128.8, 128.71, 128.69, 94.7, 81.2, 80.2, 77.7, 73.4, 72.4, 69.4, 67.4, 65.1, 58.2, 54.4, 50.7, 44.1, 40.6, 37.9, 28.6, 28.3, 27.7, 24.6; MS (ESI) m/z [M + H]$^+$ calcd for $C_{40}H_{55}N_8O_{10}$ 807.4, found 807.3.

(5*R*,6*R*,7*S*,8*R*,9*R*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-hydroxy-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (11). To a solution of **5** (23.0 mg, 0.029 mmol, 1.0 equiv) in methylene chloride (6.0 mL) was added vanadyl acetylacetonate (9.6 mM in methylene chloride, 0.59 mL, 5.66 μmol, 0.19 equiv) at 23 °C. After the mixture was stirred for 5 min, *tert*-butyl hydroperoxide (5.5 M in decane, 8.4 μL, 0.046 mmol, 1.6 equiv) was added, and the reaction mixture was then stirred at 23 °C for 16 h before being quenched with a solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v), washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by HPLC (Atlantis dC18 OBD, 19 × 150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 65% B, T = 35 min: 83% B, 5.0 mL/min; retention time: 28.5 min) to give **11** as a colorless oil (14.2 mg, 60% yield): ^{1}H NMR (600 MHz, benzene-d_6, 65 °C) δ 8.78 (s, 1H), 7.37−7.04 (m, 10H), 5.11 (d, J = 10.3 Hz, 1H), 5.09−5.03 (m, 3H), 4.63 (s, 2H), 4.37−4.29 (m, 1H), 4.03 (d, J = 12.0 Hz, 1H), 3.90−3.80 (m, 1H), 3.57−3.47 (m, 1H), 3.39 (dd, J = 9.6, 5.8 Hz, 1H), 3.37−3.29 (m, 1H), 3.28−3.21 (m, 1H), 3.19 (dd, J = 12.8, 5.2 Hz, 1H), 3.06−2.96 (m, 1H), 2.79−2.66 (m, 1H), 2.62−2.52 (m, 1H), 1.54 (s, 3H), 1.49 (s, 9H), 1.43 (s, 9H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, benzene-d_6, 65 °C) δ 172.6, 163.5, 160.9, 157.2, 153.3, 138.4, 137.6, 128.7, 128.5, 128.5, 128.2, 94.2, 81.1, 80.6, 80.2, 73.5, 72.3, 68.7, 67.1, 64.8, 58.0, 52.9, 46.9, 41.7, 40.6, 37.3, 28.5, 28.4, 27.5, 23.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{40}H_{55}N_8O_{10}$ 807.4036, found 807.4050.

(5*S*,6*R*,7*S*,8*R*,9*R*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-hydroxy-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (12). To a 25 mL round-bottom flask charged with 4 Å molecular sieves (powder, 450 mg) and methylene chloride (2.1 mL) were added titanium(IV) isopropoxide (0.20 M in methylene chloride, 1.1 mL, 0.22 mmol, 2.5 equiv) and *tert*-butyl hydroperoxide (5.5 M in decane, 52 μL, 0.286 mmol, 3.3 equiv) at −20 °C. After the mixture was stirred at −20 °C for 30 min, a solution of **5** (70.0 mg, 0.088 mmol, 1.0 equiv) in methylene chloride (1.0 mL) was added. The reaction was warmed to 23 °C and stirred for 16 h before being quenched with a solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v), washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by HPLC (Atlantis dC18 OBD, 19 × 150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 40 min: 90% B, 5.0 mL/min; retention time: 21.8 min) to give **12** as a colorless oil (31.2 mg, 44% yield): ^{1}H NMR (600 MHz, DMSO-d_6, 40 °C) δ 8.94 (brs, 1H), 7.41−7.25 (m, 10H), 7.15 (brs, 1H), 5.62 (d, J = 6.4 Hz, 1H), 5.05 (d, J = 12.6 Hz, 1H), 5.01 (d, J = 12.6 Hz, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.26−4.06 (m, 1H), 3.88 (dd, J = 11.8, 6.5 Hz, 1H), 3.83 (dd, J = 9.7, 6.0 Hz, 1H), 3.67−3.58 (m, 1H), 3.56 (dd, J = 12.5, 5.6 Hz, 1H), 3.39−3.27 (m, 2H), 3.19−3.03 (m, 1H), 2.75−2.62 (m, 1H), 2.59−2.43 (m, 2H), 1.47 (s, 3H), 1.45 (s, 9H), 1.42 (s, 9H), 1.38 (s, 3H); ^{1}H NMR (600 MHz, CD_3CN, 50 °C) δ 8.64 (s, 1H), 7.43−7.23 (m, 10H), 5.84−5.58 (m, 1H), 5.10 (d, J = 12.5 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 5.04 (d, J = 10.7 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.59 (s, 2H), 4.19−4.11 (m, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.86 (dd, J = 9.7, 6.0 Hz, 1H), 3.62−3.52 (m, 2H), 3.45−3.38 (m, 1H), 3.39−3.34 (m, 2H), 2.81−2.68 (m, 1H), 2.66−2.50 (m, 1H), 2.36−2.22 (m, 1H), 1.53 (s, 3H), 1.50 (s, 9H), 1.49 (s, 9H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN, 50 °C) δ 175.6, 162.9, 160.3, 156.7, 153.6, 138.0, 137.6, 128.7, 128.5, 128.1, 128.1, 127.9, 127.9, 94.6, 80.8, 79.4, 78.6, 72.5, 71.5, 68.5, 66.3, 57.0, 52.5, 47.9, 46.2, 39.4, 37.5, 27.8, 27.7, 26.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{40}H_{55}N_8O_{10}$ 807.4036, found 807.4049.

(5*S*,6*R*,7*S*,8*R*,9*R*)-6-((*R*)-1-Azido-2-benzoyloxyethyl)-7-(azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-2-(benzoylimino)-9-(benzoyloxy)-1,3-diazaspiro[4.4]nonan-4-one (13). To a 16 mL vial charged with **12** (30.0 mg, 0.037 mmol) in methylene chloride (0.6 mL) was added a solution of trifluoroacetic acid in methylene chloride (1:4 v/v, 1.2 mL). After being stirred at 23 °C for 80 min, the volatiles were removed by azeotrope with toluene. To a solution of the resulting amino alcohol in methanol (3.9 mL) were added copper(II) sulfate (1.66 mM in water, 0.43 mL, 0.72 μmol, 0.02 equiv) and potassium

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carbonate (31.0 mg, 0.225 mmol, 6.1 equiv) followed by freshly prepared trifluoromethanesulfonyl azide[14] (0.25 M, 0.59 mL, 0.147 mmol, 4.0 equiv) at 23 °C. After the mixture was stirred at 23 °C for 30 min, the solvents were removed by rotary evaporation. The residue was then dissolved in ethyl acetate, washed successively with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, concentrated, and separated in two batches. To two 4 mL vials each charged with the crude bisazide (15 mg, 0.0185 mmol, 1.0 equiv) obtained above and 4-bromobenzoic acid (23 mg, 0.114 mmol, 6.2 equiv) in *N*,*N*-dimethylformamide (0.6 mL) were added hydroxybenzotriazole (15.6 mg, 0.115 mmol, 6.2 equiv) and *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (23.0 mg, 0.12 mmol, 6.5 equiv) at 23 °C. After the mixture was stirred at 23 °C for 16 h, the volatiles were removed in vacuo (0.1 mmHg). The two batches were then combined and purified by HPLC (Atlantis dC18 OBD, 19 × 150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 80% B, T = 31 min: 98% B, 5.0 mL/min; retention time: 27.9 min) to afford **13** as a pale yellow solid (20.0 mg, 47% yield over three steps). Slow evaporation of a solution of **13** in methylene chloride/acetone/hexanes gave a single crystal suitable for X-ray analysis: ^{1}H NMR (400 MHz, CD_3CN) δ 9.78 (s, 1H), 8.03−7.82 (m, 4H), 7.75−7.50 (m, 6H), 7.46−7.15 (m, 12H), 5.84 (t, J = 6.2 Hz, 1H), 5.35 (d, J = 11.6 Hz, 1H), 5.18 (d, J = 11.0 Hz, 1H), 5.13 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.51 (dd, J = 11.7, 3.8 Hz, 1H), 4.38 (dd, J = 11.7, 8.3 Hz, 1H), 4.18−4.09 (m, 1H), 3.72 (dd, J = 12.6, 4.8 Hz, 1H), 3.63 (dd, J = 12.6, 7.7 Hz, 1H), 3.45−3.31 (m, 2H), 3.02−2.89 (m, 1H), 2.79−2.72 (m, 1H), 2.65−2.54 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 178.5, 175.9, 166.0, 165.9, 161.3, 157.3, 138.9, 138.0, 136.4, 132.9, 132.8, 132.4, 132.2, 132.2, 132.1, 129.6, 129.4, 129.3, 129.3, 128.9, 128.9, 128.7, 128.6, 128.5, 127.9, 80.7, 72.2, 71.6, 70.0, 67.1, 66.9, 60.9, 52.4, 48.5, 45.9, 40.0, 38.3; MS (ESI) m/z $[M + H]^+$ calcd for $C_{48}H_{42}Br_3N_{10}O_9$ 1139.1, found 1139.0.

(5*S*,6*R*,7*S*,8*R*,9*S*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-hydroxy-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (14). To a solution of **12** (1.0 mg, 1.2 μmol, 1.0 equiv) in methylene chloride (0.2 mL) was added Dess−Martin periodinane (9 mg, 0.021 mmol, 17.5 equiv) followed by a mixture of water and methylene chloride (1:1000 v/v, 32 μL) at 23 °C. After the mixture was stirred at 23 °C for 5 h, the reaction was quenched with a mixture of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v), and the volatiles were removed by rotary evaporation. The resulting residue was then dissolved in ethyl acetate, washed successively with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. To a solution of the resulting crude **17** in ethanol (0.2 mL) was added sodium borohydride (0.12 N in ethanol, 10 μL, 1.2 μmol, 1.0 equiv) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction was quenched with acetone, and the organic solvent was removed by rotary evaporation. The resulting aqueous mixture was then extracted with ethyl acetate, and the organic layer was washed successively with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, concentrated, and purified by HPLC (Eclipse XDB-C18, 9.4 × 250 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 20 min: 90% B, 4.8 mL/min; retention time: 14.1 min) to give **14** as a colorless oil (0.7 mg, 70% yield over two steps): ^{1}H NMR (600 MHz, DMSO-d_6, 50 °C) δ 9.39 (s, 1H), 7.41−7.24 (m, 10H), 6.90 (s, 1H), 5.63 (s, 1H), 5.06 (d, J = 12.6 Hz, 1H), 5.00 (d, J = 12.6 Hz, 1H), 4.94 (s, 2H), 4.56 (d, J = 11.8 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.28 (dd, J = 6.7, 6.7 Hz, 1H), 4.10−3.97 (m, 1H), 3.96−3.86 (m, 1H), 3.70 (d, J = 12.7 Hz, 1H), 3.45 (dd, J = 12.8, 4.0 Hz, 1H), 3.44−3.35 (m, 1H), 3.31−3.22 (m, 1H), 3.21−3.11 (m, 1H), 2.42−2.34 (m, 1H), 2.24−2.10 (m, 2H), 1.52 (s, 3H), 1.45 (s, 9H), 1.45 (s, 9H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 50 °C) δ 175.1, 161.2, 158.3, 156.2, 152.6, 137.5, 136.9, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 93.8, 80.0, 77.8, 72.0, 70.3, 67.5, 65.2, 56.3, 52.2, 46.5, 43.2, 39.3, 38.5, 27.8, 27.7, 26.3, 23.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{40}H_{55}N_8O_{10}$ 807.4036, found 807.4054.

(5*R*,6*R*,7*S*,8*R*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-oxo-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (16). To a solution of **11** (21.0 mg, 0.026 mmol, 1.0 equiv) in methylene chloride (3.0 mL) was added Dess−Martin periodinane (33 mg, 0.078 mmol, 3.0 equiv) followed by water (0.94 μL, 0.052 mmol, 2.0 equiv) at 23 °C. After the mixture was stirred at 40 °C for 3.5 h, the reaction was quenched with a mixture of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v), and the organic solvent was removed by rotary evaporation. The resulting aqueous mixture was extracted with ethyl acetate, and the organic layer was washed successively with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated to afford **16**. Ketone **16** was characterized after reduction to **8** by sodium borohydride as the ^{1}H NMR spectra of **16** shows a series of broad peaks presumably due to ketone/hydrate equilibrium.

(5*S*,6*R*,7*S*,8*R*)-7-(Azidomethyl)-3-(benzyloxymethyl)-8-((((benzyloxy)carbonyl)amino)methyl)-9-oxo-6-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-2-(*tert*-butoxycarbonylimino)-1,3-diazaspiro[4.4]nonan-4-one (17). To a vial charged with **16** obtained above was added acetic acid (0.2 mL) at 23 °C. After the mixture was stirred at 45 °C for 16 h, acetic acid was removed in vacuo (0.1 mmHg) and purified by HPLC (Eclipse XDB-C18, 9.4 × 250 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 20 min: 90% B, 4.8 mL/min; retention time: 13.5 min for **16** and 15.1 min for **17**) to give **16** as a colorless oil (7.0 mg, 33% yield over two steps) and **17** as a colorless oil (6.4 mg, 30% yield over two steps). Ketone **17** was characterized after reduction to **14** by sodium borohydride as the ^{1}H NMR spectra of **17** shows a series of broad peaks presumably due to ketone/hydrate equilibrium.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02266.

NMR spectra for all new compounds (PDF)

X-ray crystallographic data of compound **13** (CIF)

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Notes

The authors declare no competing financial interest.

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