Progress Towards the Syntheses of Bactobolin A and C4-*epi*-Bactobolin A Using a Sulfamate-Tethered *Aza*-Wacker Cyclization Strategy

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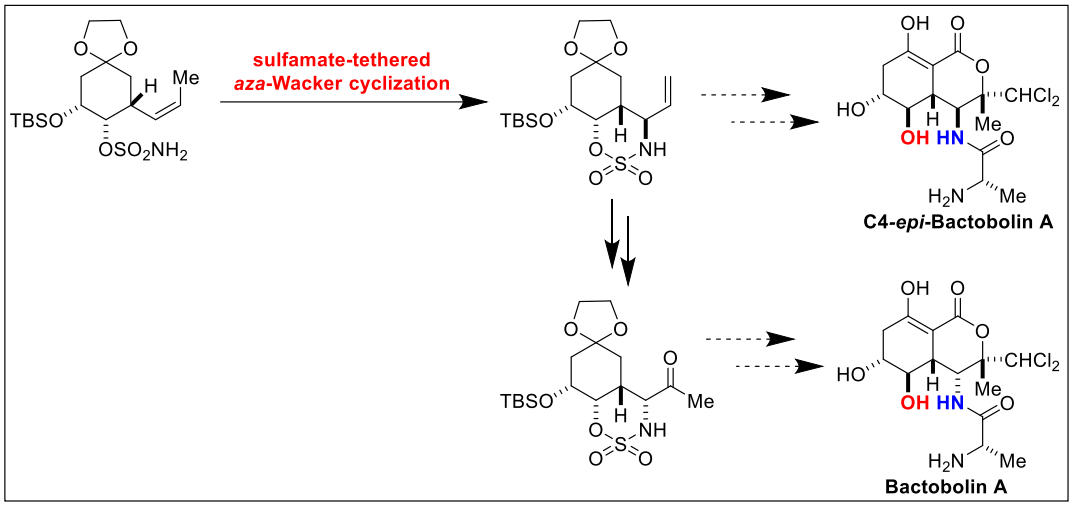


Abstract

We present a progress report towards Bactobolin A and C4-*epi*-Bactobolin A. Sulfamate-tethered *aza*-Wacker cyclization followed by a Tsuji-Wacker ketone synthesis furnishes a key tricyclic intermediate which we hypothesize can be elaborated into C4-*epi*-Bactobolin A. Epimerization of one of the stereocenters of this compound furnishes an intermediate which we hypothesize can be elaborated into Bactobolin A.

The rise of antimicrobial resistance has motivated the search for new classes of antibiotics.[1, 2] Synthetic exploration of antibiotic scaffolds is a proven strategy for enriching the therapeutic pipeline.[3-6] Our laboratory has a programmatic focus on the development of new reactions for the syntheses of antibiotics with mechanisms of action distinct from ones which are FDA-approved.[7-9] Bactobolin A is one such antibiotic which we were motivated to pursue, both for its broad-spectrum antibacterial activity and for its complex, functional-group rich scaffold (**Figure 1A**).[10, 11] Bactobolin A inhibits bacterial protein translation by binding to the L2 protein of the bacterial ribosome 50s subunit, which is an unusual location for antibiotic interactions.[12, 13] To date, there exists one racemic synthesis[14-16] (Weinreb) and one enantiospecific synthesis[17] (Švenda) of Bactobolin A (**Figure 1B**). Creative albeit unfinished approaches to Bactobolin A have been furnished by Danishefsky,[18] Fraser-Reid,[19] and Ward.[20]

There are only a few reports on the syntheses and analyses of Bactobolin A derivatives.[21-23] Existing reports have focused on modifying Bactobolin A side chains rather than fundamentally altering the core scaffold. Based on our previous efforts with a model compound,[9] we envisioned a synthesis of Bactobolin A in which our laboratory's sulfamate-tethered *aza*-Wacker cyclization[7] would be used to install the 1,3-amino alcohol structural element. We hypothesized that such a route may also be amenable to furnishing unnatural isomers of Bactobolin A (**Figure 1**) which would be difficult or impossible to access by chemical degradation or by semisynthetic studies with fermentation-derived natural product. Here, we describe our synthesis of key tricyclic intermediates using this strategy, which we envision can later be elaborated into Bactobolin A and interesting analogues.

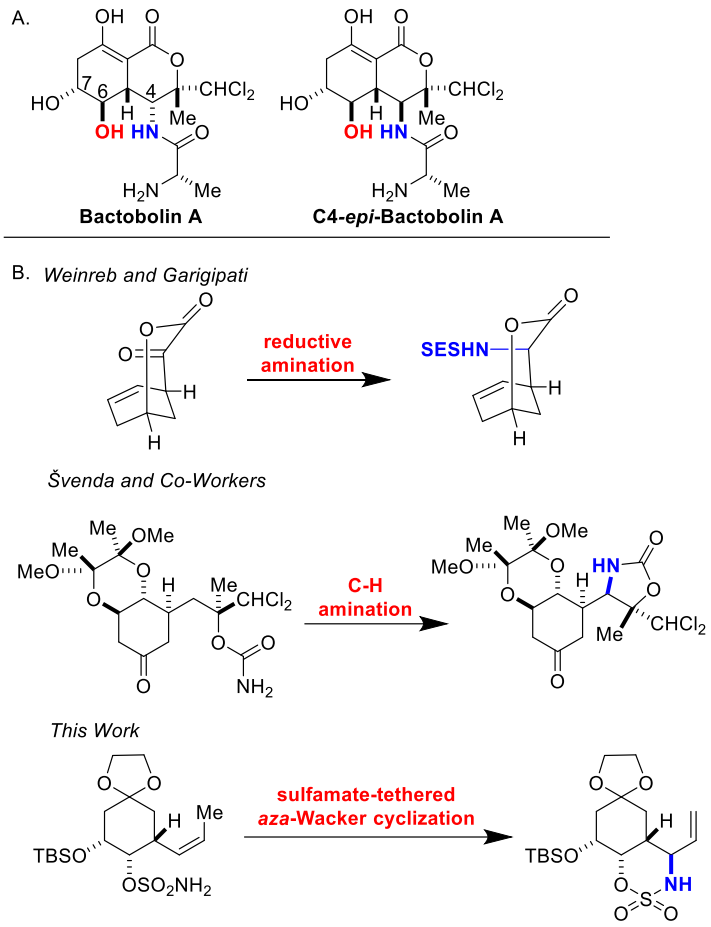


Figure 1. (A) Bactobolin A is a potent antibiotic, and there are many analogues which are unexplored. (B) Literature approaches to installing the C4 nitrogen contrasted with our own.

In our retrosynthetic analysis (**Figure 2**), we envisioned nucleophilic opening of activated oxathiazinane heterocycle **B** to set the C6 stereocenter of Bactobolin A. Tricyclic intermediate **B** would be synthesized by addition of $CHCl_2^-$ into ketone **C** followed by a Weinreb-inspired alkoxycarbonylation reaction.[16] Ketone **C** would be prepared from sulfamate **D** using two sequential Wacker oxidations. The first would be our laboratory's sulfamate-tethered *aza*-Wacker cyclization reaction followed by a Tsuji-Wacker ketone synthesis.[24] We planned to prepare sulfamate **D** using enone **E**, itself accessible from D-(-)-Quinic acid, a commercially available chiron.

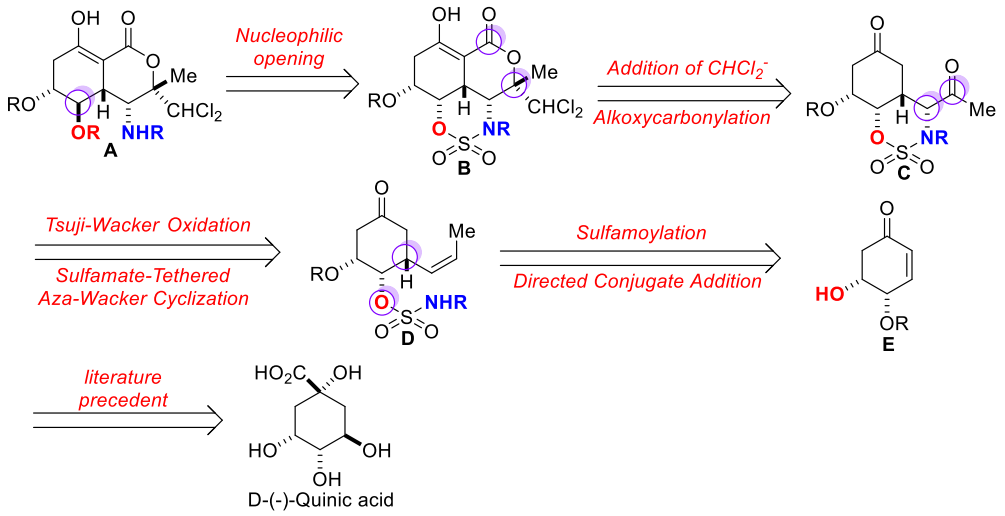


Figure 2. Our retrosynthetic analysis incorporates two Wacker oxidation steps.

Our synthesis commenced by transforming (D)-(-)-Quinic acid into enone **1** using our laboratory's previously disclosed optimization of literature precedent (**Figure 3**).[9] The acetonide group was removed by treatment of **1** with aqueous acetic acid at room temperature. Preferential TBS protection of the allylic alcohol was effected using TBSCl/imidazole/DMAP in DMF.

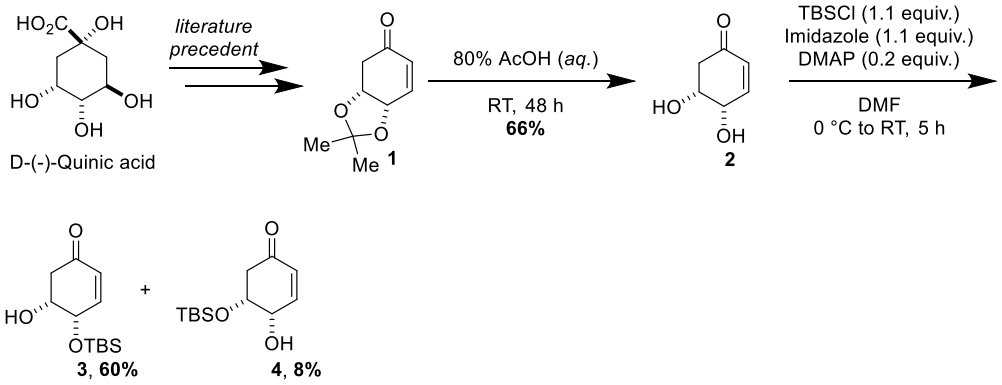
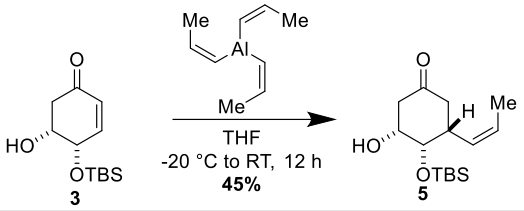


Figure 3. Opening sequence.



Entry	Reaction Conditions	Yield
1	tri((*Z*)-prop-1-en-1-yl)aluminum (3 equiv.) THF, 0 °C to RT, 12 h	10%
2	tri((*Z*)-prop-1-en-1-yl)aluminum (5 equiv.) THF, 0 °C to RT, 12 h	20%
3	tri((*Z*)-prop-1-en-1-yl)aluminum (7 equiv.) THF, 0 °C to RT, 12 h	25%
4	tri((*Z*)-prop-1-en-1-yl)aluminum (10 equiv.) THF, 0 °C to RT, 12 h	41%
5	tri((*Z*)-prop-1-en-1-yl)aluminum (12 equiv.) THF, 0 °C to RT, 12 h	35%
6	tri((*Z*)-prop-1-en-1-yl)aluminum (10 equiv.) THF, -20 °C to RT, 12 h	45%
7	tri((*Z*)-prop-1-en-1-yl)aluminum (10 equiv.) THF, -78 °C to RT, 12 h	46%

Figure 4. Conjugate addition directed by a homoallylic alcohol.

Our first major challenge in this synthesis was installation of the all-*syn* stereotriad of **5**. We hypothesized that diastereoselectivity in this conjugate addition may be achievable if addition were directed by the unprotected homoallylic alcohol of **3**. There is literature precedent for diastereoselectivity in conjugate additions in which an allylic alcohol serves as a stereocontrol element, but, to our knowledge, very little is known about chelation to a homoallylic alcohol.[25, 26] Accordingly, many conditions were tested (**Figure 4**). Early experiments with organocuprates yielded intractable mixtures of diastereomers. A positive result came upon switching to organoaluminum reagents, prepared from reaction of the corresponding Grignard reagent with $AlCl_3$. With three equivalents of tri((Z)-prop-1-en-1-yl)aluminum, we isolated desired product in 10% yield, but, more importantly, as a single diastereomer (**Figure 4**, **Entry 1**). As equivalents of tri((Z)-prop-1-en-1-yl)aluminum increased, so too did the yield (**Figure 4**, **Entries 2-4**). More than 10 equivalents of tri((Z)-prop-1-en-1-yl)aluminum was deleterious however (**Figure 4**, **Entry 5**). Dropping the start temperature of the reaction from 0 °C to –20 °C was beneficial (**Figure 4**, **Entry 6**), but there was no benefit to further decreasing the temperature to –78 °C (**Figure 4**, **Entry 7**). To confirm the stereochemistry of **5**, we prepared its acetate derivative, assigned the shifts of the salient protons using

2-D NMR spectroscopy, and saw a strong transannular nOe enhancement between these protons (see Supporting Information for further details).

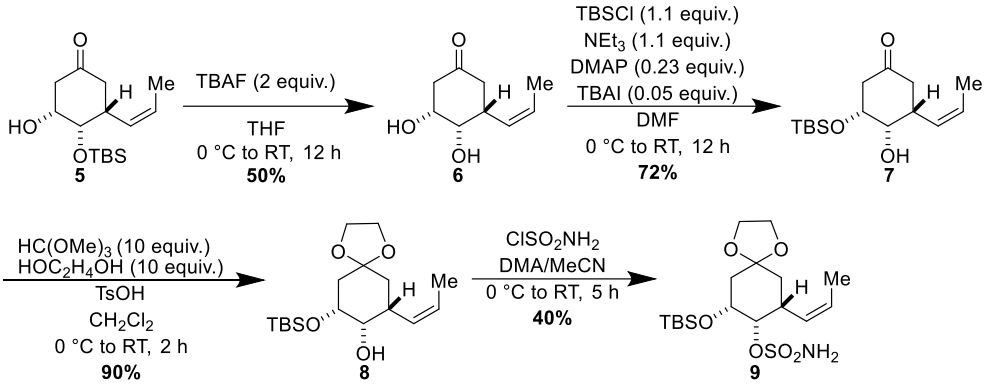
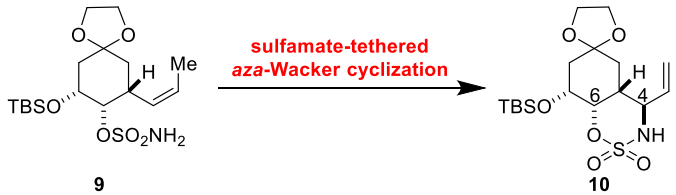


Figure 5. Synthesis of the *aza*-Wacker cyclization precursor.

Treatment of **5** with TBAF removed the TBS group (**Figure 5**). The homoallylic alcohol was then selectively protected using TBSCl/NEt_3. Ketone **7** was converted into acetonide **8** with trimethyl orthoformate, ethylene glycol, and catalytic *p*-toluenesulfonic acid. Sulfamoylation of **8** proceeded upon treatment with $ClSO_2NH_2$ in DMA.



Entry	Reaction Conditions	Yield
1	$Pd(OAc)_2$ (15 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 16 h	20%
2	$Pd(OAc)_2$ (25 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 16 h	45%
3	$Pd(OAc)_2$ (50 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 16 h	35%
4	$Pd(OAc)_2$ (25 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 24 h	50%
5	$Pd(OAc)_2$ (25 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 36 h	60%
6	$Pd(OAc)_2$ (25 mol%), $Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.), MeCN, 55 °C, 48 h	60%

Figure 6. Sulfamate-tethered *aza*-Wacker cyclization reaction.

The next challenge of the synthesis was optimization of the key sulfamate-tethered *aza*-Wacker cyclization reaction. Despite their remarkable utility for site-selective amination, *aza*-Wacker reactions are rarely used as key steps in the syntheses of complex molecules.[27, 28] Tethered *aza*-Wacker reactions

are particularly powerful because a pre-existing C–N bond is no longer required to form a new one. Our laboratory has a programmatic focus on increasing the prominence of tethered aza-Wacker technology in complex molecule syntheses, and our pursuit of Bactobolin A provided a perfect opportunity to further develop the sulfamate-tethered variant of this chemistry. With 15 mol% of $Pd(OAc)_2$ and 1 equivalent of $Cu(OAc)_2$, cyclized product was isolated in a 20% yield (**Figure 6**, **Entry 1**). Increasing the loading of $Pd(OAc)_2$ to 25 mol% led to an increase in product yield to 45% (**Figure 6**, **Entry 2**). While further [Pd] loading was deleterious (**Figure 6**, **Entry 3**), increasing the reaction time from 16 hours to 24 hours was markedly beneficial (**Figure 6**, **Entry 4**). The reaction yield plateaued at 36 hours (**Figure 6**, **Entries 5–6**). Based on previous work with a model compound,[9] we hypothesized that the newly formed C4 stereocenter was epimeric to that of natural Bactobolin A. Further experimentation (*vide infra*) would confirm this suspicion.

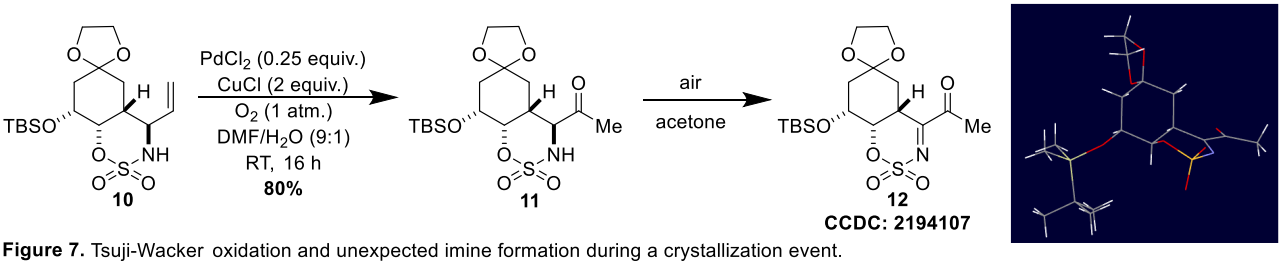


Figure 7. Tsuji-Wacker oxidation and unexpected imine formation during a crystallization event.

Tsuji-Wacker oxidation of alkene **10** into ketone **11** proceeded in excellent yield using $PdCl_2$/CuCl in aqueous DMF (**Figure 7**). We made many attempts to crystallize **11**, but, in most cases, we were unsuccessful. In one instance, high quality crystals formed from slow evaporation from acetone in a scintillation vial open to air (~14 days). However, to our surprise, the crystals were of imine **12**, which we hypothesize formed from slow oxidation of **11**.

In the Weinreb synthesis of Bactobolin A, the $CHCl_2$ moiety was diastereoselectively introduced *via* addition of Cl_2CHLi in the presence of $CeCl_3$ at –100 °C.[16] We hypothesized that finding alternate conditions for introduction of the $CHCl_2$ group may contribute to the future scalability and reproducibility

of our synthesis. To this end, we tested conditions developed by Mioskowski for the addition of CCl_3^- into ketones.[29] To our surprise, rather than forming **13**, these conditions led to inversion of the C4 stereocenter; we note that this stereochemistry matches that found in natural Bactobolin A. A crystal structure of **14** allowed us to confirm product identity and stereochemistry unambiguously. Furthermore, we were then able to assign the stereochemistry of **11** by analogy (see Supporting Information for further details).

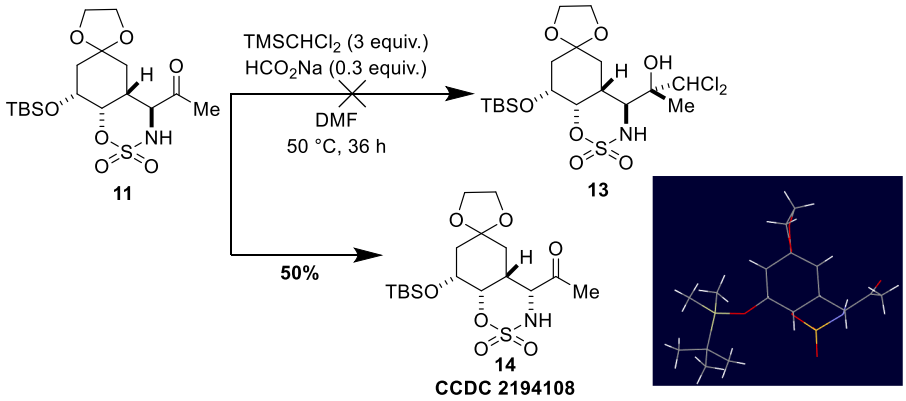


Figure 8. Conditions which should allow for $CHCl_2$ addition into the ketone actually led to epimerization of the nitrogen stereocenter.

We envision that **11** and **13** will serve as key intermediates for syntheses of C4-*epi*-Bactobolin A and Bactobolin A. Some important future steps will be diastereoselective introduction of the $CHCl_2$ functional group, formation of the lactone, and oxathiazinane ring opening. We shall continue forward with these goals in mind.

Experimental Section

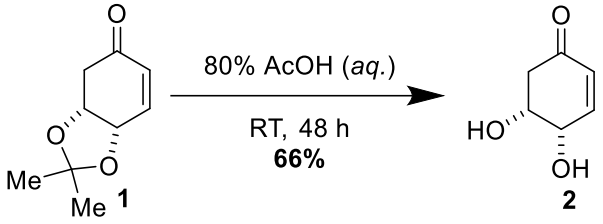
General Considerations: All reagents were obtained commercially unless otherwise noted. Solvents were purified by passage under 10 psi N_2 through activated alumina columns. Infrared (IR) spectra were recorded on a Thermo Scientific™ Nicolet™ iS™5 FT-IR Spectrometer; data are reported in frequency of absorption (cm^{-1}). ^1H NMR spectra were recorded at 400, 500, or 600 MHz. Data are recorded as: chemical shift in ppm referenced internally using residual solvent peaks, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances), integration, coupling constant

(Hz). ^{13}C NMR spectra were recorded at 101 MHz or at 126 MHz . Exact mass spectra were recorded using an electrospray ion source (ESI) either in positive mode or negative mode and with a time-of-flight (TOF) analyzer on a Waters LCT PremierTM mass spectrometer and are given in m/z. TLC was performed on pre-coated glass plates (Merck) and visualized either with a UV lamp (254 nm) or by dipping into a solution of $KMnO_4$–K_2CO_3 in water followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) or Florisil (60-100 mesh).

Synthesis and Characterization:

Compound 1 was synthesized from D-(-)-Quinic acid according to a previously reported sequence.[9]

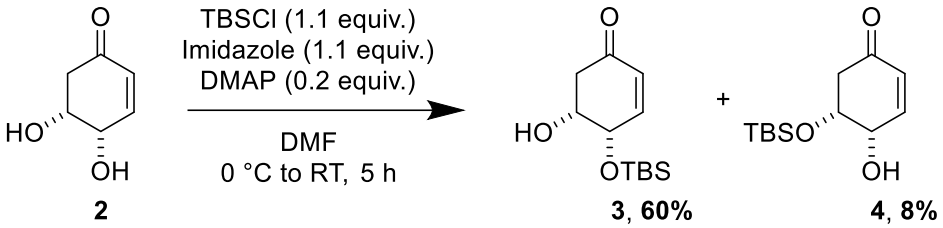
Synthesis of **Compound 2**



A 100 mL round-bottom flask was charged with a stir bar, **1** (2 g, 11.9 mmol, 1 equiv.), and 80% aqueous acetic acid (40 mL) at room temperature. The resulting solution was stirred at room temperature for 48 hours. Following this time, the solvent was removed under reduced pressure. The residue was purified through column chromatography on Florisil by eluting with hexane/ethyl acetate (20:80) to afford of **2** (1 g, 7.8 mmol, 66%) as a white semi-solid.

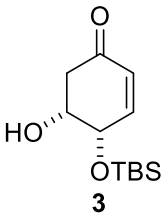
2 is a known compound.[30]

Synthesis of **Compounds 3** and **4**



2 **3**, **60%** **4**, **8%**

A 100 mL round-bottom flask was charged with **2** (1.00 g, 7.81 mmol, 1 equiv.), imidazole (0.584 g, 8.59 mmol, 1.1 equiv.), and anhydrous DMF (15 mL, Reaction Concentration = 0.5 M). The reaction flask was cooled to 0 °C using an ice-water bath. TBSCl (1.30 g, 8.63 mmol, 1.1 equiv.) and DMAP (190 mg, 1.56 mmol, 0.2 equiv.) were sequentially added. The reaction mixture was stirred for 2 hours at 0 °C. Following this time, the ice-water bath was removed, and the reaction was allowed to warm to room temperature over a period of 3 hours. Following this time, the reaction was diluted with EtOAc (30 mL) and chilled H_2O (50 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 X 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (2 X 20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (hexanes/ethyl acetate, 85/15) to afford **3** (colorless oil, 1.13 g, 4.64 mmol, 60%) and **4** (white solid, 0.151 g, 0.623 mmol, 8%).

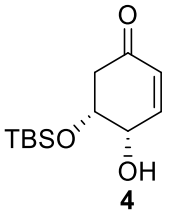


3

(4*S*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-hydroxycyclohex-2-en-1-one

Compound 3: $[\alpha]_D$ = +191.8 ° (c = 1, $CHCl_3$).; FT-IR: 3054, 2960, 1730, 1474, 652 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 – 6.53 (m, 1H), 6.06 – 5.98 (m, 1H), 4.57 – 4.51 (m, 1H), 4.21 (dq, *J* = 3.2, 1.7 Hz, 1H), 2.84 – 2.73 (m, 1H), 2.52 (ddd, *J* = 16.7, 3.2, 0.9 Hz, 1H), 0.93 (s, 9H), 0.17 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR

(101 MHz, $CDCl_3$) δ 196.4, 147.4, 129.9, 70.0, 68.7, 42.4, 25.8, 18.2, -4.43, -4.64.; HRMS (ESI) m/z = [M + Na^+] calculated for $C_{12}H_{22}O_3SiNa$ = 265.1236, Found Mass = 265.1265 (10 ppm error).

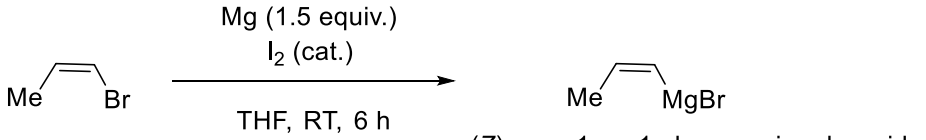


4

(4*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxycyclohex-2-en-1-one

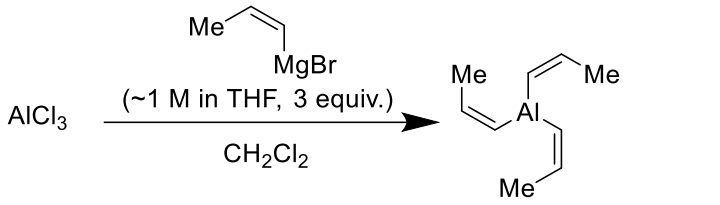
Compound 4: $[\alpha]_D$ = +107.0 ° (c = 1, $CHCl_3$).; FT-IR: 3056, 2954, 2860, 1717, 1473, 650.9 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.67 (m, 1H), 6.04 (ddd, *J* = 10.3, 1.8, 0.9 Hz, 1H), 4.38 (ddd, *J* = 3.7, 3.1, 1.8 Hz, 1H), 4.33 (dddd, *J* = 4.6, 3.6, 3.1, 1.5 Hz, 1H), 2.73 (ddd, *J* = 16.2, 6.0, 1.0 Hz, 1H), 2.55 (dd, *J* = 16.3, 3.1 Hz, 1H), 0.88 (s, 9H), 0.11 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.7, 148.0, 130.1, 70.8, 67.8, 44.0, 25.8, 18.1, -4.4, -4.7.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{12}H_{22}O_3SiNa$ = 265.1236, Found Mass = 265.1263 (10 ppm error).

Synthesis of **Compound 5**



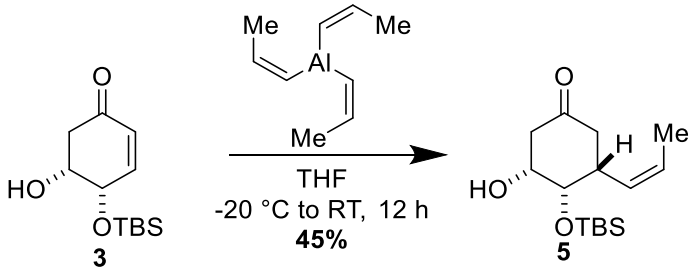
(*Z*)-prop-1-en-1-ylmagnesium bromide

An oven-dried 500 mL two-neck round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. The flask was evacuated and backfilled with N_2. Mg turnings (4.4 g, 183 mmol, 1.5 equiv.), a few crystals of iodine, and anhydrous THF (124 mL) were added. Next, *Cis*-1-bromo-1-propene (10.6 mL, 15.1 g, 125 mmol) was slowly added (Caution! There is a significant exotherm during Grignard reagent formation, which may lead to THF reflux). The mixture was stirred at room temperature for 6 hours.

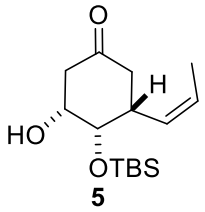


tri((*Z*)-prop-1-en-1-yl)aluminum

A 500 mL round-bottom flask was charged with a stir-bar, $AlCl_3$ (5.5 g, 41.2 mmol, 1 equiv.), and anhydrous CH_2Cl_2 (20 mL). The mixture was cooled to 0 °C using an ice-water bath. Freshly prepared (Z)-prop-1-en-1-ylmagnesium bromide solution (1 M in THF, 124 mL, 124 mmol, 3 equiv.) was added over a period of one hour, and the mixture was allowed to warm to room temperature over a period of 12 hours.



A 500 mL round-bottom flask was charged with a stir-bar, **3** (1 g, 4.13 mmol, 1 equiv.), and anhydrous THF (10 mL). The reaction mixture was cooled to -20 °C using an ice-salt water bath. Freshly prepared tri((Z)-prop-1-en-1-yl)aluminum (0.3 M in THF, 138 mL, 41.3 mmol, 10 equiv.) was slowly added. The reaction mixture was allowed to warm to room temperature over a period of 12 hours. Following this time, the reaction mixture was cooled to 0 °C using an ice-water bath and quenched with slow addition of 20% aqueous tartaric acid solution (40 mL). After transferring to a separatory funnel, the mixture was extracted with ethyl acetate (2 X 100 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel by eluting with hexane/ethyl acetate (80/20) to afford **5** (0.529 g, 1.86 mmol, 45% yield) as a brown oil.

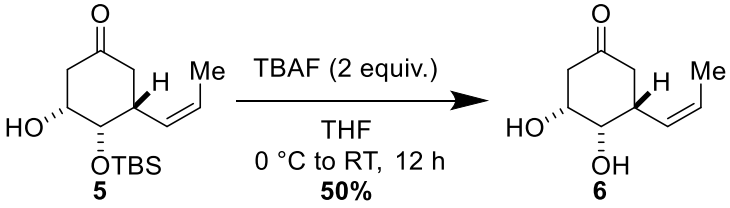


5

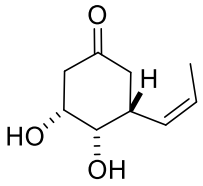
(3*R*,4*S*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-5-((*Z*)-prop-1-en-1-yl)cyclohexan-1-one

Compound 5: $[\alpha]_D$ = +15 ° (c = 1, $CHCl_3$).; FT-IR: 3440, 3012, 2958,1717, 1473 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.49 (m, 1H), 5.45 – 5.35 (m, 1H), 3.99 (t, *J* = 2.2 Hz, 1H), 3.88 (ddd, *J* = 11.6, 5.1, 2.4 Hz, 1H), 2.74 – 2.57 (m, 2H), 2.57 – 2.48 (m, 2H), 2.10 – 2.01 (m, 1H), 1.61 (dd, *J* = 6.8, 1.8 Hz, 3H), 0.95 (s, 9H), 0.14 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.4, 130.3, 125.6, 73.5, 72.2, 45.5, 41.0, 36.6, 26.2, 18.6, 13.2, -3.7, -4.0.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{15}H_{28}O_3SiNa$ = 307.1705, Found Mass = 307.1723 (6 ppm error).

Synthesis of **Compound 6**



A 50 mL round-bottom flask was charged with a magnetic stir bar, **5** (568 mg, 2 mmol, 1 equiv.), and THF (10 mL). The reaction mixture was cooled to 0 °C using an ice-water bath. TBAF (1 M in THF, 4 mL, 4 mmol, 2 equiv.) was added, and the reaction mixture was warmed to room temperature over a period of 12 h. Following this time, the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography on Florisil by eluting with hexane/ethyl acetate (30/70 mixture) to afford **6** (brown oil, 0.170 g, 1 mmol, 50%).

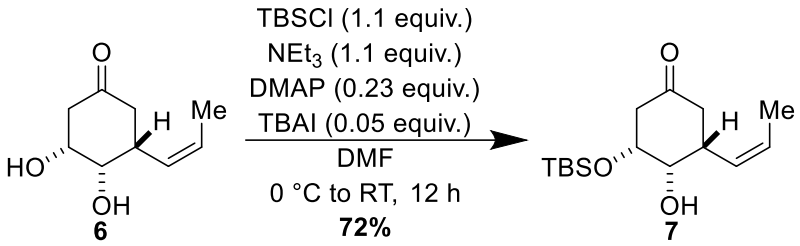


6

(3*R*,4*S*,5*R*)-3,4-dihydroxy-5-((*Z*)-prop-1-en-1-yl)cyclohexan-1-one

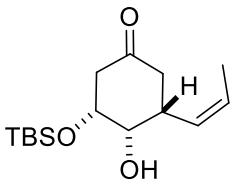
Compound 6: $[\alpha]_D$ = +3.82 ° (c = 1, $CHCl_3$).; FT-IR: 3440, 3426, 2932, 1714, 1042 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 – 5.46 (m, 2H), 3.99-3.95 (m, 2H), 2.83 – 2.68 (m, 2H), 2.68 – 2.50 (m, 2H), 2.43 (s, 1H), 2.34 (s, 1H), 2.10 (ddd, *J* = 14.2, 4.5, 2.1 Hz, 1H), 1.63 (dd, *J* = 6.6, 1.6 Hz, 3H).;$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.8, 129.1, 126.3, 71.6, 71.4, 44.8, 40.6, 35.8, 13.2.; HRMS calculated for $C_9H_{14}O_3SiNa$ = 193.0841, Found Mass = 193.0837 (2 ppm error).

Synthesis of **Compound 7**



A 50 mL round-bottom flask was charged with a magnetic stir-bar, **6** (0.64 g, 3.76 mmol, 1.00 equiv.), and anhydrous DMF (10 mL). The reaction flask was cooled to 0 °C using an ice-water bath. Tetrabutylammonium iodide (TBAI) (69 mg, 0.189 mmol, 0.05 equiv.), TBSCl (626 mg, 4.15 mmol, 1.10 equiv.), NEt_3 (0.63 mL, 0.457 g, 4.52 mmol, 1.20 equiv.), and DMAP (105 mg, 0.86 mmol, 0.23 equiv.) were added sequentially. After warming to room temperature over a period of 12 hours, the reaction mixture was again cooled to 0 °C using an ice-water bath and quenched with chilled H_2O (20 mL). The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (2 X 20 mL). The organic layers were combined, washed once with saturated aqueous NaCl solution, and dried with Na_2SO_4. After the solvent was removed under reduced pressure, the resulting residue was purified by column

chromatography on silica gel by eluting with hexane/ethyl acetate (80/20) to afford **7** (colorless oil, 0.770 g, 2.71 mmol, 72% yield).

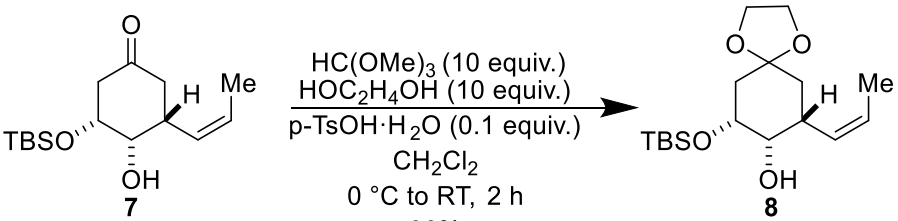


7

(3*R*,4*S*,5*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5-((*Z*)-prop-1-en-1-yl)cyclohexan-1-one

Compound 7: $[\alpha]_D$ = +9.0 ° (c = 1, $CHCl_3$).; FT-IR: 3423, 2950, 2830, 1710, 1473, 1136, cm^{-1}.;^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 – 5.53 (m, 2H), 3.95 (ddd, *J* = 11.0, 5.5, 2.7 Hz, 1H), 3.81 (t, *J* = 2.6 Hz, 1H), 2.77 – 2.56 (m, 3H), 2.49 – 2.39 (m, 1H), 2.12 – 2.00 (m, 1H), 1.65 – 1.57 (m, 3H), 0.90 (s, 9H), 0.09 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.8, 129.5, 125.5, 72.5, 71.9, 45.4, 40.7, 35.5, 25.8, 18.1, 13.1, -4.5, -4.7.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{15}H_{28}O_3SiNa$ = 307.1705, Found Mass = 307.1722 (6 ppm error).

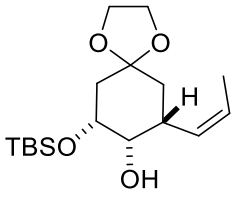
Synthesis of **Compound 8**



7 **8**

A 50 mL round-bottom flask was charged with a magnetic stir-bar, **7** (0.3 g, 1.05 mmol, 1 equiv.) and anhydrous CH_2Cl_2 (10 mL). The reaction flask was cooled to 0 °C using an ice-water bath. Trimethyl orthoformate (1.15 mL, 1.12 g, 10.5 mmol, 10 equiv.), ethylene glycol (0.6 mL, 0.67 g, 10.7 mmol, 10 equiv.), and *p*-TsOH·H_2O (18 mg, 0.09 mmol, 0.1 equiv.) were added at 0 °C. The reaction mixture was warmed to room temperature over a period of 2 hours. Following this time, the reaction mixture was

cooled to 0 °C using an ice-water bath and quenched with chilled H_2O (15 mL). After transferring to a separatory funnel, the mixture was extracted with CH_2Cl_2 (2 X 15 mL). The combined organic layers were washed once with saturated aqueous NaCl solution and dried with Na_2SO_4. After the solvent was removed under reduced pressure, the resulting residue was purified by chromatography on silica gel by eluting with hexane/ethyl acetate (85:15) to afford **8** (colorless oil, 0.311 g, 0.95 mmol, 90% yield).

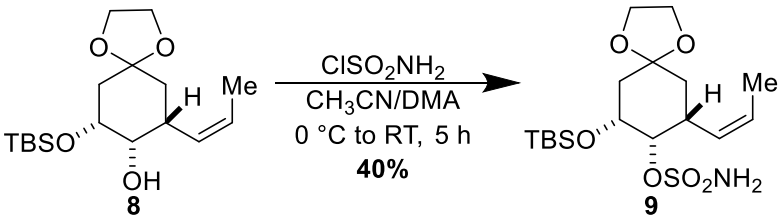


8

(7*R*,8*S*,9*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-((*Z*)-prop-1-en-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol

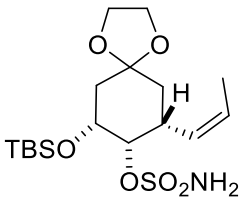
Compound 8: $[\alpha]_D$ = –16.5 ° (c = 1, $CHCl_3$).; FT-IR: 3420, 2930, 2840, 1473, 1036, 650.9 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 – 5.42 (m, 2H), 3.95 (p, *J* = 2.7 Hz, 4H), 3.91 – 3.85 (m, 1H), 3.65 (t, *J* = 2.7 Hz, 1H), 2.69 (dddd, *J* = 12.8, 8.5, 4.2, 2.5 Hz, 1H), 1.97 – 1.78 (m, 2H), 1.72 – 1.67 (m, 1H), 1.66 – 1.62 (m, 3H), 1.38 (ddd, *J* = 13.0, 4.2, 2.5 Hz, 1H), 0.89 (s, 9H), 0.08 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 130.9, 124.5, 108.9, 72.0, 71.4, 64.5, 64.3, 37.7, 34.7, 33.9, 25.9, 18.2, 13.2, -4.5, -4.7.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{17}H_{32}O_4SiNa$ = 351.1968, Found Mass = 351.1984 (5 ppm error).

Synthesis of **Compound 9**



8 **9**

Compound 9: A 5 mL microwave vial was charged with a stir bar and chlorosulfonyl isocyanate ($ClSO_2NCO$) (0.18 mL, 0.30 g, 2.14 mmol, 2.5 equiv.) and cooled to 0 °C using an ice-water bath. Formic acid (0.08 mL, 0.098 g, 2.15 mmol, 2.5 equiv.) was slowly added (Caution! Vigorous gas evolution during addition), and the mixture was stirred for 10 minutes, during which a white solid formed. Anhydrous acetonitrile (4 mL) was added to this solid. The resulting solution was stirred at room temperature for 12 h. After 12 h, the reaction mixture was cooled to 0 °C using an ice-water bath, and alcohol **8** (0.28 g, 0.854 mmol, 1 equiv.) dissolved in 0.6 mL of DMA was added dropwise using a syringe. The resulting solution was warmed to room temperature over 5 h. Subsequently, the reaction was quenched with ice water (10 mL) and transferred to a separatory funnel. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 65:35) to afford 140 mg (0.34 mmol, 40%) of **9** as a white solid.



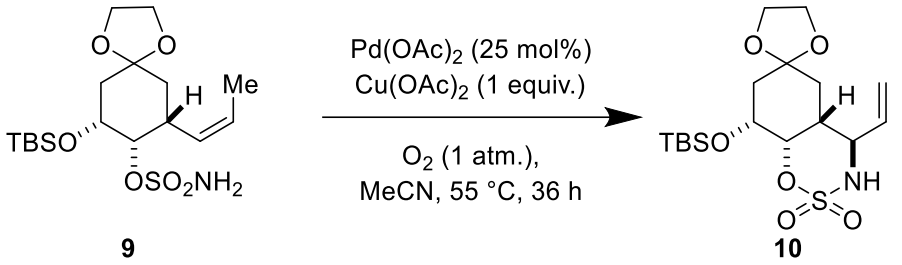
9

(7*R*,8*S*,9*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-((*Z*)-prop-1-en-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl sulfamate

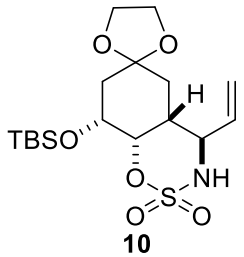
Compound 9: $[\alpha]_D = -11.5$ ° (c = 1, $CHCl_3$).; FT-IR: 3260, 2857, 1673, 1473, 1036 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.51 (m, 1H), 5.50 – 5.39 (m, 1H), 5.25 (s, 2H), 4.74 (s, 1H), 4.05 (ddd, *J* = 12.1, 5.0, 2.5 Hz, 1H), 4.02 – 3.89 (m, 4H), 2.88 – 2.72 (m, 1H), 2.07 – 1.95 (m, 1H), 1.85 – 1.78 (m, 1H), 1.74 (t, *J* = 13.3 Hz, 1H), 1.69 – 1.60 (m, 3H), 1.48 (ddd, *J* = 13.5, 4.5, 2.4 Hz, 1H), 0.93 (s, 9H), 0.21 – 0.11 (m, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 128.5, 126.2, 108.1, 85.9, 71.8, 64.7, 64.6, 38.3, 34.9, 34.2, 26.0, 18.7, 13.3, -4.9, -5.1.;

HRMS (ESI) m/z = [M + Na+] calculated for $C_{17}H_{33}NO_6SSiNa$ = 430.1696, Found Mass = 430.1716 (5 ppm error).

Synthesis of **Compound 10**



A 20 mL microwave vial containing a magnetic stir-bar was charged with sulfamate **9** (140 mg, 0.343 mmol, 1 equiv.), $Pd(OAc)_2$ (19 mg, 0.085 mmol, 0.25 equiv.), and $Cu(OAc)_2$ (63 mg, 0.347 mmol, 1 equiv.) in 6.8 mL of acetonitrile (final concentration 0.05 M). The reaction vial was sealed and then evacuated and backfilled with oxygen three times. The reaction vessel was then submerged in an oil bath preheated to 55 °C and kept at this temperature under a balloon of O_2 (~1 atm) for 36 h. After 36 h, the reaction mixture was cooled to room temperature and filtered through a small plug of silica. The silica plug was further rinsed with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 65:35) to afford 83 mg (0.205 mmol, 60%) of **10** as a white solid.

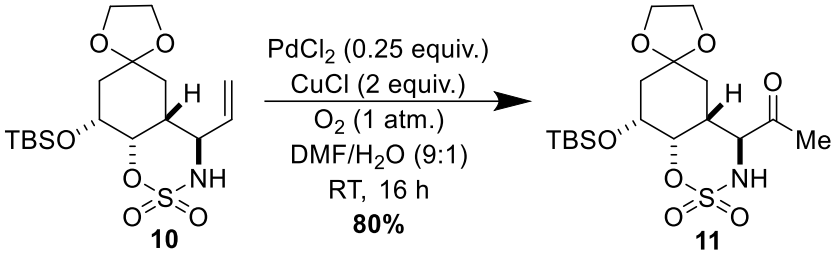


10

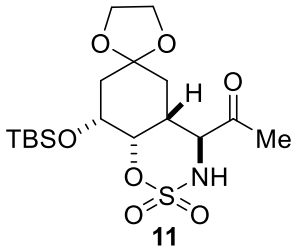
(4*R*,4a*R*,8*R*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-4-vinylhexahydro-5*H*-spiro[benzo[*e*][1,2,3]oxathiazine-6,2'-[1,3]dioxolane] 2,2-dioxide

Compound 10: $[\alpha]_D$ = +41.0 ° (c = 1, $CHCl_3$); FT-IR: 3264, 2926, 1180, 654 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (ddd, *J* = 17.4, 10.7, 6.0 Hz, 1H), 5.36 – 5.25 (m, 2H), 4.94 (t, *J* = 2.2 Hz, 1H), 4.75 (d, *J* = 5.8 Hz, 1H), 3.97 (dddd, *J* = 11.7, 7.8, 4.8, 2.0 Hz, 5H), 3.78 (tt, *J* = 6.0, 1.7 Hz, 1H), 2.10 – 1.90 (m, 3H), 1.82 (dddd, *J* = 12.9, 4.9, 2.4, 0.8 Hz, 1H), 1.58 – 1.49 (m, 1H), 0.88 (s, 9H), 0.09 (overlapping singlets, 6H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.6, 117.9, 107.9, 81.4, 69.2, 64.8, 64.7, 61.2, 38.4, 33.6, 33.5, 25.8, 18.2, -4.5.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{17}H_{31}NO_6SSiNa$ = 428.1539, Found Mass = 428.1500 (9 ppm error).

Synthesis of **Compound 11**



A 5 mL microwave vial was charged with a magnetic stir bar, **10** (81 mg, 0.2 mmol, 1 equiv.), 2 mL of DMF/H_2O (9:1 mixture), $PdCl_2$ (9 mg, 0.05 mmol, 0.25 equiv.), and CuCl (40 mg, 0.4 mmol, 2 equiv.). The resulting dark brown suspension was stirred under a balloon of O_2 (~1 atm) for 16 h. After 16 h, the reaction was quenched with ice water (10 mL) and transferred to a separatory funnel. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The resulting residue was purified through silica gel column chromatography (hexane/ethyl acetate = 60:40) to afford 68 mg (0.16 mmol, 80%) of **11** as a white solid.

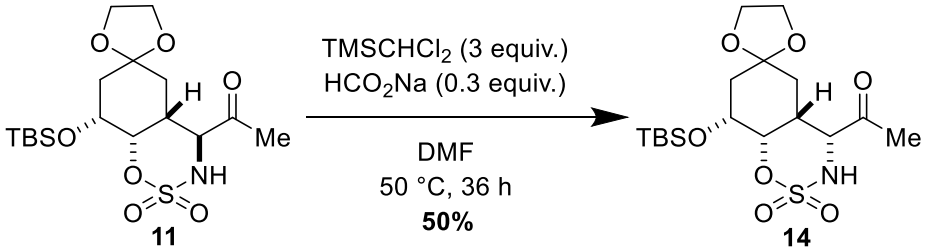


11

1-((4*S*,4a*R*,8*R*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2,2-dioxidohexahydro-5*H*-spiro[benzo[*e*][1,2,3]oxathiazine-6,2'-[1,3]dioxolan]-4-yl)ethan-1-one

Compound 11: $[\alpha]_D$ = 20.6 ° (c = 1, $CHCl_3$).; FT-IR: 3185, 2932, 1715, 1438, 1073 cm^{-1}.; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (d, *J* = 7.0 Hz, 1H), 4.82 (d, *J* = 2.6 Hz, 1H), 4.08 – 3.86 (m, 5H), 3.57 (dd, *J* = 6.9, 1.6 Hz, 1H), 2.67 (ddt, *J* = 14.0, 4.4, 1.8 Hz, 1H), 2.43 (s, 3H), 2.03 – 1.77 (m, 3H), 1.46 – 1.36 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 203.8, 107.7, 83.1, 68.8, 66.6, 64.8, 64.7, 38.3, 32.6, 27.5, 27.1, 25.8, 18.2, -4.59, -4.57.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{17}H_{31}NO_7SSiNa$ = 444.1488, Found Mass = 444.1455 (7 ppm error).

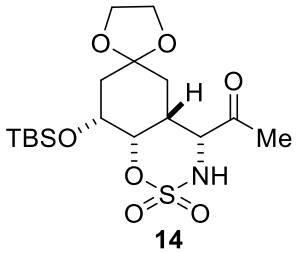
Synthesis of **Compound 14**



11 **14**

To a solution of **11** (30 mg, 0.071 mmol, 1 equiv.) in dry DMF (1 mL) was added $TMSCHCl_2$ (0.032 mL, 0.033 g, 0.212 mmol, 3 equiv.) and HCO_2Na (1.5 mg, 0.022 mmol, 0.3 equiv.) at room

temperature. The resulting solution was heated to 50 °C using an oil bath and stirred at this temperature for 36 h. Following this time, reaction was cooled to room temperature. Subsequently, MeOH (1 mL) and a 1 M aqueous HCl solution (1 mL) were added. The reaction mixture was stirred at room temperature for 1 h and then poured into saturated aqueous NH_4Cl solution (10 mL). After transferring to a separatory funnel, this mixture was extracted with Et_2O (2 X 15 mL). The combined organic layers were washed once with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The resulting residue was purified through column chromatography on silica gel using hexane/ethyl acetate (80:20) as an eluent to afford 15 mg (0.036 mmol, 50%) of **14** as a white solid.



14

1-((4*R*,4a*R*,8*R*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2,2-dioxidohexahydro-5*H*-spiro[benzo[*e*][1,2,3]oxathiazine-6,2'-[1,3]dioxolan]-4-yl)ethan-1-one

Compound 14: $[\alpha]_D$ = 15.6 ° (c = 1, $CHCl_3$).; FT-IR: 3185, 2932, 1715, 1438, 1073 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, *J* = 9.8 Hz, 1H), 4.92 (s, 1H), 4.65 (dd, *J* = 9.7, 3.2 Hz, 1H), 4.05 – 3.90 (m, 5H), 2.29-2.26 (m, 1H), 2.25 (s, 3H), 1.96 (t, *J* = 12.4 Hz, 1H), 1.82 (ddd, *J* = 4.9, 2.3, 0.8 Hz, 1H), 1.70 (t, *J* = 13.4 Hz, 1H), 1.07 – 0.96 (m, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.1, 107.5, 83.7, 68.9, 64.9, 64.8, 64.7, 38.0, 31.5, 28.0, 27.0, 25.8, 18.2, -4.50, -4.53.; HRMS (ESI) m/z = [M + Na+] calculated for $C_{17}H_{31}NO_7SSiNa$ = 444.1488, Found Mass = 444.1459 (7 ppm error).

Acknowledgements

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