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Total Synthesis of Buergerinin F and Buergerinin G

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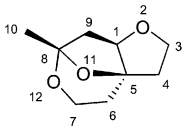
Abstract: Syntheses of buergerinin F (**1**) and buergerinin G (**2**) were carried out to establish the absolute stereochemistry of these natural products. A linear sequence was used to synthesize **1** in 15 steps and 9% overall yield from thymidine. Subsequent oxidation of **1** with ruthenium tetroxide afforded **2** in 77% yield.

In 2000, Zhu and co-workers reported[1] the isolation of two new natural products, buergerinin F (**1**) and buergerinin G (**2**) (Chart 1), from *Scrophularia buergeriana*, one of a number of *Scrophularia* species that are used in Asian herbal medicine.[2] To date, the biological activity of these molecules has not been established. The structures and relative stereochemistry of these compounds were determined using NMR spectroscopy and, in the case of **2**, X-ray crystallography. However, the absolute stereochemistry of neither species was established. We report here the first total syntheses of these natural products, and establish that the stereochemistry is 1*R*,5*S*,8*S* in **1** and 1*R*,5*R*,8*S* in **2**.

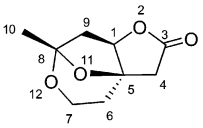
Our synthesis of **1** and **2** (Scheme 1) began with the known glycal **3**, which was prepared in two steps and 65% yield from thymidine.[3] Hydrogenation of the double bond in **3** afforded alcohol **4**, which was then oxidized with pyridinium chlorochromate to provide **5** in 78% yield over the two steps. Subsequent treatment of **5** with vinylmagnesium bromide at −78 °C afforded tertiary alcohol **6** in 94% yield. The stereochemistry at the quaternary center in **6** was established by NOE experiments. Irradiation of the vinyl group hydrogens gave NOEs to hydrogens on both endocyclic methylene carbons. In addition, no NOE was observed between the vinyl hydrogens and those attached to the exocyclic methylene carbon. Taken together, these data point to the vinyl substituent in **6** being oriented *trans* to the *tert*-butyldiphenylsiloxymethyl group.

Having established the stereochemistry in **6**, this product was converted, in 96% yield, to diol **7** via hydroboration. Protection of the diol as an ethylidene acetal was achieved in 79% yield by reaction of **7** with ethyl vinyl ether and *p*-TsOH. A 12:1 inseparable mixture of diastereomers was formed. We also synthesized isopropylidene acetal **9** from **7** in good yield using standard methods (2,2-dimethoxypropane, *p*-TsOH), thus producing a product with a nonstereogenic ketal carbon. However, the acetonide protecting group was not stable to a subsequent transformation, and thus, we proceeded instead from **8**.

CHART 1



1



2

With a route to compound **8** in place, we continued toward the targets by cleaving the silyl ether, affording alcohol **10** in 92% yield. Subsequent treatment of **10** with tosyl chloride and triethylamine afforded **11**, which, when exposed to *n*-Bu_4NI, provided iodide **12**. Reaction of **12** with vinylmagnesium bromide gave the allylfuran **13**. These transformations all proceeded efficiently, and the conversion of **10** into **13** was achieved in 74% overall yield. Attempts to synthesize allylfuran **13** directly from tosylate **11** were unsuccessful.

The final oxygen atom was introduced via a Wacker oxidation. Thus, treatment[4] of **13** with $PdCl_2$, CuCl, and O_2 afforded the desired ketone **14** together with an inseparable byproduct. In the ^{1}H NMR spectrum of this mixture of compounds, a small triplet at 9.76 ppm (J = 1.5 Hz) was present, which we attribute to aldehyde **15**. We could not, however, separate this byproduct as a pure compound for characterization, and thus, we cannot unequivocally prove its identity. If the assumption is made that this byproduct is **15**, an 8:1 mixture of ketone/aldehyde was formed in the Wacker oxidation, in 64% combined yield. A number of methods were explored, unsuccessfully, for separation of these compounds by chromatography. We also treated the mixture with ethylene glycol and *p*-TsOH, but the resulting dioxolane derivatives were still chromatographically inseparable. We were, however, able to successfully separate these compounds after reduction of the crude product with sodium borohydride. At this stage, we obtained alcohol **16** as a single isomer[5] in 70% yield. We could not, however, isolate the reduced byproduct, presumably **17**, in quantities large enough for characterization.

With pure alcohol **16** in hand, the synthesis of **1** was completed in two steps. First, alcohol **16** was oxidized using pyridium chlorochromate, yielding ketone **14** in 91% yield. Finally, hydrolysis of the acetal in refluxing

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(1) Lin, S. J.; Jiang, S. H.; Li, Y. M.; Zeng, J. F.; Zhu, D. Y. *Tetrahedron Lett.* **2000**, *41*, 1069.

(2) For example, see: (a) Kim, S. R.; Lee, K. Y.; Koo, K. A.; Sung, S. H.; Lee, N. G.; Kim, J.; Kim, Y. C. *J. Nat. Prod.* **2002**, *65*, 1696. (b) Qian, J.; Hunkler, D.; Rimpler, H. *Phytochemistry* **1992**, *31*, 905. (c) Kim, S. R.; Kim, Y. C. *Phytochemistry* **2000**, *54*, 503 and references therein.

(3) Cameron, M. A.; Cush, S. B.; Hammer, R. P. *J. Org. Chem.* **1997**, *62*, 9065.

(4) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9.

(5) We did not determine the stereochemistry at either the ethylidene acetal or alcohol carbons.

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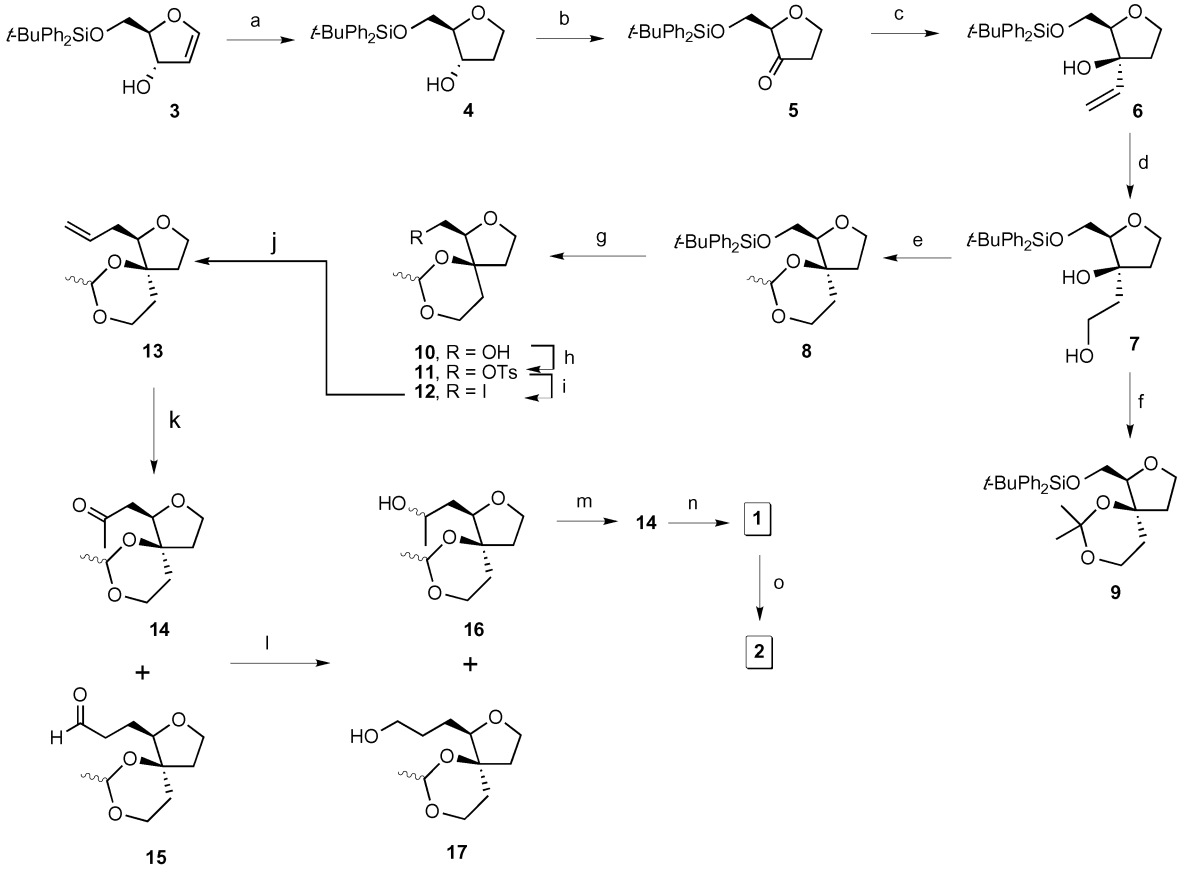
SCHEME 1[a]



[a] Reagents and conditions: (a) H_2, Pd/C, CH_3OH, rt, 87%; (b) PCC, NaOAc, CH_2Cl_2, rt, 90%; (c) vinylmagnesium bromide, THF, −78 °C, 94%; (d) 9-BBN, THF, 0 °C → rt, then NaOH, H_2O_2, 0 °C, 96%; (e) ethyl vinyl ether, *p*-TsOH, CH_2Cl_2, rt, 79%; (f) 2,2-dimethoxypropane, *p*-TsOH, rt, 92%; (g) *n*-Bu_4NF, THF, rt, 92%; (h) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 96%; (i) *n*-Bu_4NI, toluene, rt, 77%; (j) vinylmagnesium bromide, THF, 0 °C → rt, quantitative; (k) O_2, $PdCl_2$, CuCl, DMF, H_2O, rt, 64%; (l) $NaBH_4$, THF, rt, 70%; (m) PCC, NaOAc, CH_2Cl_2, rt, 91%; (n) HOAc, H_2O, reflux, quantitative; (o) $RuCl_3 \cdot H_2O$, $NaIO_4$, $NaHCO_3$, CCl_4, acetonitrile, H_2O, rt, 77%.

aqueous acetic acid afforded buergerinin F (**1**) in quantitative yield.[6] Starting from thymidine, the target was obtained in 9% overall yield in 15 steps. Oxidation of **1** with ruthenium tetroxide provided buergerinin G (**2**) in 77% yield.

We are unsure as to the origin of the high regioselectivity observed in the oxidation of **1** to **2**. Previous work[7] on the mechanism of ruthenium tetroxide oxidation of ethers has led to the proposal that the reaction proceeds via a concerted mechanism (Figure 1), and that the transition state is a five-membered ring adduct (e.g., **19**) involving the substrate and oxidant. We first speculated that the oxidized carbon, C-3 in **1** (Chart 1), is more accessible to the oxidant than C-7. However, molecular mechanics calculations on **1** (data not shown) did not show C-7 to be substantially more hindered than C-3. It

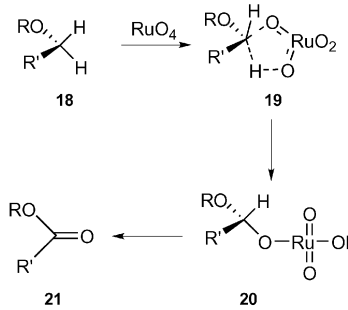


FIGURE 1. Proposed mechanism for RuO_4 oxidation of ethers (see ref 7).

is also possible that the necessary ring flattening that must occur in the proposed transition state is more readily accommodated in the furan ring containing C-3 than in the pyran ring containing C-7, which is part of a rigid bicyclic framework.

The NMR spectra for both **1** and **2** closely matched those previously reported[1] for the natural products (see the Supporting Information). The optical rotation measured for synthetic **1** ($[\alpha]_D$ +39.1, *c* 0.9, $CHCl_3$) was nearly identical to that reported for the material isolated from *S. buergeriana* ($[\alpha]_D$ +40.67, *c* 0.431, $CHCl_3$), thus establishing the stereochemistry in **1** as 1*R*,5*S*,8*S*. The

(6) We also explored the possibility of preparing **1** directly from the mixture of **14** and **15**. Although we were successful in obtaining **1**, the material was contaminated with an inseparable byproduct, which we believe is the cyclized product analogous to **1** that is produced from **15**. In the ^1H NMR spectrum of the product obtained from the hydrolysis of the mixture of **14** and **15** was a small doublet of doublets at 5.23 ppm (J = 5.6, 2.4 Hz). We propose that this resonance arises from the acetal hydrogen in the byproduct.

(7) (a) Bakke, J. M.; Frøhaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 310. (b) Bakke, J. M.; Frøhaug, A. E. *Acta Chem. Scand.* **1995**, *49*, 615.

magnitude of the optical rotation measured for synthetic **2** ($[\alpha]_D$ +33.2, *c* 1.0, $CHCl_3$) matched the value reported for the isolated natural product ($[\alpha]_D$ +47.71, *c* 0.509, $CHCl_3$) less well. However, the signs of both rotations are the same, and we therefore, propose that the stereochemistry in **2** is 1*R*,5*R*,8*S*.

In conclusion, we describe here the first total syntheses of buergerinin F (**1**) and buergerinin G (**2**) via a linear route starting from thymidine. These syntheses allowed us to not only confirm the proposed structures but also identify the absolute configuration of these natural products.

Experimental Section

General Procedures. See ref 8.

(2*S*,3*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)tetrahydrofuran-3-ol (4). Alkene **3** (1.56 g, 4.4 mmol) was dissolved in CH_3OH (20 mL), and Pd/C (100 mg) was added. The reaction mixture was stirred overnight under H_2 and filtered through Celite followed by rinsing with methanol. The crude product was purified by chromatography (2:1 hexane/EtOAc) to give **4** as a colorless syrup (1.37 g, 87%): R_f 0.32 (2:1 hexane/EtOAc); $[\alpha]_D$ +14.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.67−7.64 (m, 4 H), 7.44−7.35 (m, 6 H), 4.40 (quintet, 1 H, J = 3.1 Hz), 3.94 (dd, 2 H, J = 8.4, 5.4 Hz), 3.82 (ddd, 1 H, J = 9.3, 4.0, 3.0 Hz), 3.75 (dd, 1 H, J = 10.5, 4.2 Hz), 3.57 (dd, 1 H, J = 10.5, 6.2 Hz), 2.13 (dtd, 1 H, J = 16.9, 8.4, 6.2 Hz), 1.87 (dtd, 1 H, J = 13.0, 5.4, 3.2 Hz), 1.78 (br s, 1 H), 1.04 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 135.57 (2 C), 135.53 (2 C), 133.22, 133.15, 129.78, 129.75, 127.40 (2 C), 127.73 (2 C), 86.06, 74.27, 67.15, 64.76, 34.83, 26.82 (3 C), 19.20; HRMS *m*/*z* calcd for $[C_{21}H_{28}O_3Si]Na^+$ 379.1700, found 379.1710.

(2*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)dihydrofuran-3-one (5). A suspension of sodium acetate (8.59 g, 63.1 mmol), PCC (6.80 g, 31.6 mmol), and 4 Å molecular sieves (4 g) in CH_2Cl_2 (200 mL) was stirred for 30 min, and then a solution of **4** (3.75 g, 10.5 mmol) in CH_2Cl_2 (60 mL) was added. The reaction mixture was stirred for 2 h, diluted with 1:1 ether/hexane (300 mL), and stirred for 30 min. This suspension was then filtered through Celite and further eluted with 1:1 ether/hexane. The eluent was concentrated, and the residue was purified by chromatography (4:1 hexane/EtOAc) to give **5** as a white solid (3.34 g, 90%), mp 79−80 °C: R_f 0.37 (4:1 hexane/EtOAc); $[\alpha]_D$ +61.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.69−7.62 (m, 4 H), 7.42−7.24 (m, 6 H), 4.50 (dt, 1 H, J = 8.8, 7.3 Hz), 4.25 (dt, 1 H, J = 8.7, 7.6 Hz), 3.94 (dd, 1 H, J = 11.0, 2.8 Hz), 3.88 (dd, 1 H, J = 11.0, 2.3 Hz), 3.84 (dd, 1 H, J = 4.8, 2.2 Hz), 2.56 (t, 2 H, J = 7.4 Hz), 1.00 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 215.21, 135.63 (2 C), 135.57 (2 C), 132.95, 132.72, 129.80, 129.74, 127.75 (4 C), 80.37, 65.86, 64.44, 37.49, 26.67 (3 C), 19.16; HRMS *m*/*z* calcd for $[C_{21}H_{26}O_3Si]Na^+$ 377.1543, found 377.1545.

(2*S*,3*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-vinyltetrahydrofuran-3-ol (6). To a stirred solution of **5** (3.34 g, 9.4 mmol) in THF (30 mL) at −78 °C was added vinylmagnesium bromide (18.8 mL, 1.0 M THF solution). The reaction mixture was stirred for 2 h at −78 °C, and then a saturated aqueous solution of NH_4Cl (150 mL) was added before the solution was extracted with ether. The organic layer was washed with brine, dried, and purified by chromatography (3:1 hexane/EtOAc) to give **6** as a colorless syrup (3.37 g, 94%): R_f 0.42 (3:1 hexane/EtOAc); $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.72−7.65 (m, 4 H), 7.42−7.38 (m, 6 H), 5.92 (dd, 1 H, J = 17.1, 10.6 Hz), 5.54 (dd, 1 H, J = 17.1, 1.5 Hz), 5.21 (dd, 1 H, J = 10.6, 1.5 Hz), 4.25 (s, 1 H), 4.16 (ddd, 1 H, J = 9.5, 8.0, 6.7 Hz), 4.00−3.88 (m, 3 H), 3.63 (dd, 1 H, J = 4.2, 3.3 Hz), 2.11−2.02 (m, 2 H) 1.04 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 140.87, 136.15 (2 C), 135.97 (2 C), 133.03, 132.65, 130.34 (2 C), 128.24 (2 C), 128.21 (2 C), 114.75, 83.61, 82.20, 67.40, 63.04, 41.93, 27.10 (3 C), 19.50; HRMS *m*/*z* calcd for $[C_{23}H_{30}O_3Si]Na^+$ 405.1856, found 405.1866.

(2*S*,3*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-(2′-hydroxyethyl)tetrahydrofuran-3-ol (7). To a stirred solution of **6** (3.15 g, 8.23 mmol) in THF (15 mL) at 0 °C was added 9-BBN (44.7 mL, 0.5 M solution in ether). The reaction mixture was warmed to rt and stirred for 3 h before being cooled again to 0 °C. To this solution was added H_2O (10 mL), followed by 2.5 M NaOH (20 mL) and 30% H_2O_2 (15 mL). The reaction mixture was stirred for 2 h and acidified with 0.3 M HCl. The product was extracted into CH_2Cl_2, and the organic layer was successively washed with a saturated solution of $NaHCO_3$ and brine before being dried and concentrated. The product was purified by chromatography (1:2 hexane/EtOAc) to give **7** as a white solid (3.15 g, 96%), mp 75−77 °C: R_f 0.46 (1:2 hexane/ EtOAc); $[\alpha]_D$ +18.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.74−7.66 (m, 4 H), 7.45−7.36 (m, 6 H), 4.08 (td, 1 H, J = 8.4, 6.8 Hz), 4.02−3.92 (m, 3 H), 3.90−3.82 (m, 2 H), 3.56 (dd, 1 H, J = 4.0, 3.4 Hz), 2.16 (ddd, 1 H, J = 12.6, 6.8, 4.0 Hz), 2.06 (ddd, 1 H, J = 14.3, 8.8, 4.4 Hz), 1.99 (ddd, 1 H, J = 14.7, 12.6, 4.0 Hz), 1.69 (ddd, 1 H, J = 14.4, 5.6, 3.6 Hz), 1.05 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 135.71 (2 C), 135.51 (2 C), 132.53, 132.18, 129.97, 129.92, 127.86 (2 C), 127.79 (2 C), 83.68, 82.80, 66.40, 63.47, 60.57, 40.28, 39.66, 26.71 (3 C), 19.06; HRMS *m*/*z* calcd for $[C_{23}H_{32}O_4Si]Na^+$ 423.1962, found 423.1959.

(1*S*,5*R*)-1-(*tert*-Butyldiphenylsilanyloxymethyl)-7-methyl-2,6,8-trioxaspiro[4.5]decane (8). To a stirred solution of **7** (520 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) were added ethyl vinyl ether (1.3 mL, 13.57 mmol) and *p*-TsOH (20 mg). After being stirred for 24 h, the reaction mixture was diluted with CH_2Cl_2 and successively washed with a saturated aqueous solution of $NaHCO_3$ and brine before being dried and concentrated. The product was purified by chromatography (3:1 hexane/EtOAc) to give **8** as a colorless syrup (440 mg, 79%) as a 12:1 ratio of isomers as determined by ^{1}H NMR. Data for major isomer: R_f 0.34 (3:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.74−7.70 (m, 4 H), 7.40−7.35 (m, 6 H), 4.81 (dd, 1 H, J = 10.0, 5.0 Hz), 4.01−3.97 (m, 3 H), 3.84−3.73 (m, 3 H), 3.60 (dd, 1 H, J = 5.6, 5.2 Hz), 2.40 (ddd, 1 H, J = 12.9, 7.5, 5.5 Hz), 2.15 (td, 1 H, J = 13.1, 5.3 Hz), 1.86 (ddd, 1 H, J = 12.9, 8.1, 7.2 Hz), 1.42 (dd, 1 H, J = 19.2, 5.7 Hz), 1.25 (d, 3 H, J = 5.0 Hz), 1.06 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 135.67 (4 C), 133.75, 133.60, 129.50 (2 C), 127.58 (4 C), 93.94, 87.24, 81.33, 66.29, 64.26, 62.29, 34.39, 31.46, 26.82 (3 C), 21.22, 19.18; HRMS *m*/*z* calcd for $[C_{25}H_{34}O_4Si]Na^+$ 449.2119, found 449.2114.

(1*S*,5*R*)-1-(*tert*-Butyldiphenylsilanyloxymethyl)-7,7-dimethyl-2,6,8-trioxaspiro[4.5]decane (9). To a stirred solution of **7** (48 mg, 0.12 mmol) in 2,2-dimethoxypropane (3 mL) was added *p*-TsOH (2 mg). The reaction mixture was stirred for 3 h, and then worked up as described for the preparation of **8**. The product was purified by chromatography (2:1 hexane/EtOAc) to give **9** as a colorless syrup (56 mg, 92%): R_f 0.52 (2:1 hexane/EtOAc); $[\alpha]_D$ +15.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.74−7.67 (m, 4 H), 7.42−7.34 (m, 6 H), 4.10−3.95 (m, 2 H), 3.89 (dd, 1 H, J = 11.1, 4.0 Hz), 3.85−3.74 (m, 3 H), 3.57 (dd, 1 H, J = 5.4, 4.2 Hz), 2.34 (ddd, 1 H, J = 12.3, 7.7, 7.4 Hz), 2.04−1.94 (m, 2 H), 1.45 (dt, 1 H, J = 10.5, 3.0 Hz), 1.42 (s, 3 H), 1.29 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 135.66 (2 C), 135.64 (2 C), 133.78, 133.67, 129.50, 129.47, 127.58 (2 C), 127.55 (2 C), 98.29, 87.82, 79.12, 66.54, 63.01, 57.42, 38.42, 31.92, 29.97, 26.81 (3 C), 24.44, 19.15; HRMS *m*/*z* calcd for $[C_{26}H_{36}O_4Si]Na^+$ 463.2275, found 463.2270.

(1*S*,5*R*)-1-(Hydroxymethyl)-7-methyl-2,6,8-trioxaspiro[4.5]decane (10). To a stirred solution of **8** (420 mg, 0.98 mmol) in THF (7 mL) was added *n*-Bu_4NF (1.2 mL, 1.0 M THF solution). The reaction mixture was stirred for 12 h and then concentrated. The product was purified by chromatography (9:1 CH_2Cl_2/CH_3OH) to give **10** as a white solid (170 mg, 92%), mp 52−54 °C. Data for major isomer: R_f 0.17 (1:6 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 4.81 (dd, 1 H, J = 10.0, 5.0 Hz), 4.11−4.02 (m, 2 H), 3.91−3.75 (m, 4 H), 3.48 (t, 1 H, J = 4.6 Hz), 2.52 (dd, 1 H, J = 7.8, 4.5 Hz), 2.33 (td, 1 H, J = 12.8, 7.3 Hz), 2.08 (td, 1 H, J = 13.1, 5.3 Hz), 1.99 (ddd, 1 H, J = 13.1,

(8) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046.

7.4, 5.9 Hz), 1.34 (td, 1 H, J = 13.3, 1.8 Hz), 1.28 (d, 3 H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 94.38, 86.17, 83.45, 66.54, 64.14, 61.16, 34.94, 32.30, 21.29; HRMS *m/z* calcd for $[C_9H_{16}O_4]Na^+$ 211.0941, found 211.0961.

(1*S*,5*R*)-1-(Tosyloxymethyl)-7-methyl-2,6,8-trioxaspiro-[4.5]decane (11). To a stirred solution of **10** (810 mg, 4.30 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added Et_3N (1.2 mL, 8.60 mmol), DMAP (1.05 g, 8.60 mmol), and *p*-TsCl (2.46 g, 12.90 mmol). After being stirred for 40 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 and worked up as described for the preparation of **8**. The product was purified by chromatography (1:1 hexane/EtOAc) to give **11** as a pale yellow syrup (1.41 g, 96%). Data for major isomer: R_f 0.55 (1:2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 7.80 (d, 2 H, J = 8.3 Hz), 7.31 (d, 2 H, J = 8.1 Hz), 4.74 (dd, 1 H, J = 10.0, 5.0 Hz), 4.33 (dd, 1 H, J = 11.0, 3.2 Hz), 4.11 (dd, 1 H, J = 11.0, 7.5 Hz), 4.02−3.94 (m, 2 H), 3.80−3.70 (m, 2 H), 3.67 (dd, 1 H, J = 7.5, 3.2 Hz), 2.42 (s, 3 H), 2.34 (ddd, 1 H, J = 13.0, 7.4, 5.7 Hz), 2.01 (td, 1 H, J = 13.1, 5.3 Hz), 1.86 (ddd, 1 H, J = 13.0, 7.2, 6.8 Hz), 1.30 (ddd, 1 H, J = 13.3, 2.1, 1.7 Hz), 1.18 (d, 3 H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 144.63, 133.15, 129.77 (2 C), 127.96 (2 C), 94.05, 84.30, 81.93, 69.08, 66.70, 63.99, 34.38, 31.35, 21.60, 21.02; HRMS *m/z* calcd for $[C_{16}H_{22}O_6S]Na^+$ 365.1029, found 365.1017.

(1*S*,5*R*)-1-(Iodomethyl)-7-methyl-2,6,8-trioxaspiro[4.5]-decane (12). To a stirred solution of **11** (1.41 g, 4.12 mmol) in toluene (20 mL) was added *n*-Bu_4NI (15.22 g, 41.20 mmol). The reaction mixture was refluxed overnight, cooled, diluted with ether (250 mL), and filtered. After concentration, the product was purified by chromatography (2:1 hexane/EtOAc) to give **12** as a yellow oil (946 mg, 77%). Data for major isomer: R_f 0.52 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 4.78 (dd, 1 H, J = 10.0, 5.0 Hz), 4.05−4.00 (m, 2 H), 3.82−3.72 (m, 3 H), 3.36 (dd, 1 H, J = 10.8, 3.2 Hz), 3.23 (dd, 1 H, J = 10.8, 9.6 Hz), 2.40 (ddd, 1 H, J = 13.2, 7.5, 6.0 Hz), 2.04 (td, 1 H, J = 13.0, 5.3 Hz), 1.96 (ddd, 1 H, J = 13.0, 7.9, 6.7 Hz), 1.30 (ddd, 1 H, J = 13.3, 2.2, 1.5 Hz), 1.25 (d, 3 H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 94.15, 87.68, 81.48, 65.76, 64.01, 34.86, 31.82, 21.14, 2.91; HRMS *m/z* calcd for $[C_9H_{15}O_3I]Na^+$ 320.9958, found 320.9944.

(1*R*,5*R*)-1-Allyl-7-methyl-2,6,8-trioxaspiro[4.5]decane (13). To a stirred solution of **12** (300 mg, 1.01 mmol) in THF (5 mL) at 0 °C was added vinylmagnesium bromide (4.0 mL, 1. 0 M THF solution). The reaction mixture was stirred for 7 h and allowed to warm to rt. The reaction was worked up as described for the preparation of **6**. The product was purified by chromatography (2:1 hexane/EtOAc) to give **13** as a colorless oil (200 mg, quantitative). Data for major isomer: R_f 0.54 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 5.91 (ddt, 1 H, J = 17.1, 10.1, 7.0 Hz), 5.12 (ddd, 1 H, J = 17.1, 3.4, 1.6 Hz), 5.04 (ddd, 1 H, J = 10.5, 2.0, 1.0 Hz), 4.80 (dd, 1 H, J = 10.0, 5.0 Hz), 4.04−3.99 (m, 2 H), 3.80−3.68 (m, 2 H), 3.36 (dd, 1 H, J = 7.2, 5.7 Hz), 2.39−2.30 (m, 3 H), 1.96 (td, 1 H, J = 13.1, 5.3 Hz), 1.88 (ddd, 1 H, J = 13.9, 8.1, 5.9 Hz), 1.27 (d, 3 H, J = 5.0 Hz), 1.23 (ddd, 1 H, J = 13.2, 2.1, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 135.92, 116.49, 93.93, 86.66, 81.20, 65.86, 64.21, 34.66, 32.91, 31.43, 21.21; HRMS *m/z* calcd for $[C_{11}H_{18}O_3]Na^+$ 221.1148, found 221.1127.

(1*R*,5*R*)-1-(2′-Oxopropyl)-7-methyl-2,6,8-trioxaspiro[4.5]-decane (14) and (*1R*,5*R*)-1-(3′-Formyloxyethyl)-7-methyl-2,6,8-trioxaspiro[4.5]decane (15). A mixture of palladium chloride (29 mg, 10 mol %) and cuprous chloride (164 mg, 1.66 mmol) in 3:1 DMF/H_2O (4 mL) was stirred for 1 h under O_2. Alkene **13** (330 mg, 1.66 mmol) in DMF (2 mL) was added dropwise. The reaction mixture was stirred for 24 h, poured into a 3 M HCl solution, and extracted into ether. The organic layer was successively washed with a saturated aqueous $NaHCO_3$ solution and brine, before being dried, and concentrated. The product was purified by chromatography (1:4 hexane/EtOAc) to give **14** as a yellow oil together with a byproduct believed to be aldehyde **15** (combined 230 mg, 64%).

(1*R*,5*R*)-1-(2′-Hydroxypropyl)-7-methyl-2,6,8-trioxaspiro-[4.5]decane (16). A mixture of **14** and **15** (70 mg, 0.33 mmol) was dissolved in THF (3 mL), and $NaBH_4$ (50 mg, 1.32 mmol) was added. The reaction mixture was stirred for 13 h, diluted with $CHCl_3$, successively washed with 0.1 M HCl, a saturated aqueous solution of $NaHCO_3$, and brine before being dried, and concentrated. The product was purified by chromatography (1:4 hexane/EtOAc) to give **16** as a yellow oil (50 mg, 70%): R_f 0.28 (1:4 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 4.83 (dd, 1 H, J = 10.0, 5.0 Hz), 4.10−3.99 (m, 3 H), 3.84−3.77 (m, 2 H), 3.55 (dd, 1 H, J = 10.1, 2.7 Hz), 2.37 (ddd, 1 H, J = 13.4, 7.8, 6.0 Hz), 1.97−1.87 (m, 2 H), 1.85−1.76 (m, 1 H), 1.69 (dt, 1 H, J = 14.9, 2.7 Hz), 1.30 (d, 3 H, J = 5.0 Hz), 1.26 (dd, 1 H, J = 2.2, 1.6 Hz), 1.23 (d, 3 H, J = 6.2 Hz), 1.20−1.13 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 94.02, 87.45, 81.52, 67.74, 66.35, 64.20, 36.44, 33.98, 31.17, 23.54, 21.21; HRMS *m/z* calcd for $[C_{11}H_{20}O_4]Na^+$ 239.1254, found 239.1236.

(1*R*,5*R*)-1-(2′-Oxopropyl)-7-methyl-2,6,8-trioxaspiro[4.5]-decane (14). A suspension of sodium acetate (188 mg, 1.38 mmol), PCC (149 mg, 0.69 mmol), and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (5 mL) was stirred for 30 min before the solution of **16** (50 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred for 2 h, and then worked up as described for the preparation of **5**. The product was purified by chromatography (1:4 hexane/EtOAc) to give **14** as a yellow oil (45 mg, 91%). Data for major isomer: R_f 0.44 (1:4 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, δ_H) 4.82 (dd, 1 H, J = 10.0, 5.0 Hz), 4.05−3.98 (m, 2 H), 3.92 (dd, 1 H, J = 8.3, 4.0 Hz), 3.83−3.75 (m, 2 H), 2.80 (dd, 1 H, J = 16.8, 8.3 Hz), 2.69 (dd, 1 H, J = 16.8, 4.0 Hz), 2.34 (ddd, 1 H, J = 12.9, 7.6, 6.4 Hz), 2.22 (s, 3 H), 1.97−1.88 (m, 2 H), 1.28 (d, 3 H, J = 5.0 Hz), 1.26−1.11 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, δ_C) 207.54, 94.02, 82.62, 81.44, 66.08, 64.16, 42.46, 34.33, 31.18, 31.02, 21.18; HRMS *m/z* calcd for $[C_{11}H_{18}O_4]Na^+$ 237.109728, found 237.10964.

Buergerinin F (1). Ketone **14** (40 mg, 0.19 mmol) was dissolved in 80% acetic acid (5 mL), and the resulting solution was stirred at 100 °C for 2 h. After cooling, the reaction mixture was concentrated and the product was purified by chromatography (6:1 → 1:1 hexane/EtOAc) to give **1** as a colorless oil (32 mg, 100%): R_f 0.43 (1:4 hexane/EtOAc); $[\alpha]_D$ +39.1 (*c* 0.9, $CHCl_3$) [lit.[1] $[\alpha]_D$ +40.67 (*c* 0.431, $CHCl_3$)]; EI-MS *m/z* calcd for $C_9H_{14}O_3^+$ 170.093746, found 170.0946. The NMR data for this compound closely matched those previously reported[1] (see the Supporting Information).

Buergerinin G (2). To a stirred solution of **1** (20 mg, 0.12 mmol) in 1:1:1 CCl_4/acetonitrile/H_2O (1.5 mL) were added sodium bicarbonate (65 mg, 0.78 mmol) and sodium periodate (140 mg, 0.65 mmol). After 15 min of vigorous stirring, ruthenium chloride hydrate (10 mg, 0.05 mmol) was added. Following 22 h of stirring, brine was added and the product was extracted with CH_2Cl_2. The organic layer was dried and concentrated, and the product was purified by chromatography (1:4 hexane/EtOAc) to give **2** as a white solid (17 mg, 77%): R_f 0.41 (1:4 hexane/ EtOAc); $[\alpha]_D$ +33.2 (*c* 1.0, $CHCl_3$) [lit.[1] $[\alpha]_D$ +47.71 (*c* 0.509, $CHCl_3$)]; EI-MS *m/z* calcd for $C_9H_{12}O_4^+$ 184.073011, found 184.0718. The NMR data for this compound closely matched those previously reported[1] (see the Supporting Information).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds and tables comparing NMR data for synthetic **1** and **2** vs those isolated from *S. buergeriana*. This material is available free of charge via the Internet at http://pubs.acs.org.

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