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Synthesis of (+)-Sulcatine G

Douglass F. Taber* and Kevin J. Frankowski

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

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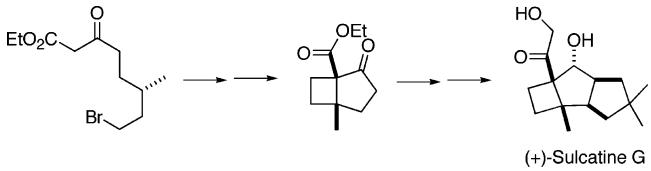
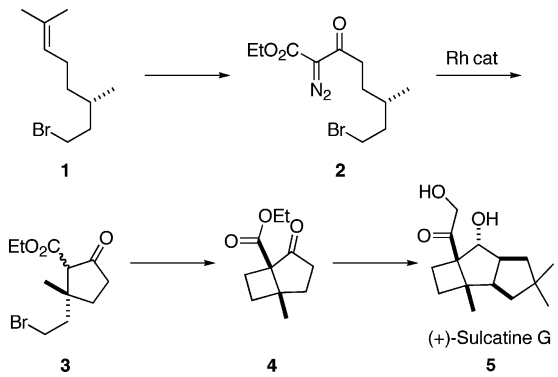


The total synthesis of (+)-sulcatine G is described. A key structural feature of sulcatine G is the highly functionalized, enantiomerically pure cyclobutane ring. We have prepared (+)-sulcatine G using a new strategy for bicyclic ring construction, Rh-mediated intramolecular C−H insertion followed by intramolecular alkylation.

Sulcatine G **5** is a tricyclic sesquiterpene isolated from cultures of the *Basidiomycetes* fungus *Laurilia sulcata*.[1] The isolated compound exhibited antifungal activity against *Cladosporium cladosporioides* and *C. cucumerinium*.[1] Sulcatine G possesses an unusual *cis*, *anti*, *cis*-tricyclo [6.2.0.0^{2,6}] decane skeleton. A key feature of sulcatine G is the highly functionalized, enantiomerically pure cyclobutane ring containing adjacent quaternary carbons. The correct absolute configuration of sulcatine G was established by Mehta through the total synthesis of the enantiomer.[2] We envisioned that the bicyclo[3.2.0] heptane core of (+)-sulcatine G could be assembled by a sequence of Rh-mediated intramolecular C−H insertion[3,4] followed by intramolecular alkylation, as illustrated (Scheme 1). The commercial availability of citronellyl bromide **1** in enantiomerically pure form made this approach particularly attractive.

Natural products such as sulcatine G that contain cyclobutanes with adjacent chiral quaternary carbons occur only sporadically. Counting sulcatine G, there are 16 skeletal classes of natural products containing this unusual structure.[5] The four others that have drawn the efforts of synthetic chemists are 2-isopropylidene-3b,6a-dimethyl-octahydro-cyclobutadicyclopenten-1-one,[9] lintenone,[7] solanoeclepin A,[8] and 3-debromoperforatone.[9]

SCHEME 1



With the exception of 3-debromoperforatone, each of the syntheses thus far reported has relied on the traditional [2 + 2] photocycloaddition. The cyclobutane of 3-debromoperforatone was synthesized using a bromonium ion cascade terminated by a hydride shift.

Results and Discussion

Preparation of Enone 7. To prepare ketone **4** (Scheme 2), we began with the commercial (*S*)-(+)-citronellyl bromide **1**. Application of Roskamp's ozonolysis/diazo coupling[10] led to the *β*-keto ester **6**. Diazo transfer using methanesulfonyl azide[11] in CH_2Cl_2 afforded the α-diazo *β*-keto ester **2**.

The construction of cyclopentane rings by Rh-mediated intramolecular C−H insertion has been well-established by this group[3] and by others.[4] We used rhodium octanoate dimer in CH_2Cl_2 at 0 °C to cyclize the α-diazo *β*-keto ester **2**, to give the enantiomerically pure cyclopentanone **3** as a mixture of diastereomers.

(1) Arnone, A.; Nasini, G.; Vajna de Pava, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2723.

(2) (a) For the synthesis of the unnatural enantiomer of sulcatine G, see: Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2002**, *43*, 3319. (b) For an earlier synthesis of racemic sulcatine G, see: Mehta, G.; Sreenivas, K. *Chem. Commun.* **2001**, 1892.

(3) (a) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276 and references therein. (b) For the first report that Rh-mediated intramolecular C−H insertion proceeds with retention of absolute configuration, see: Taber, D. F.; Petty, Eric, H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.

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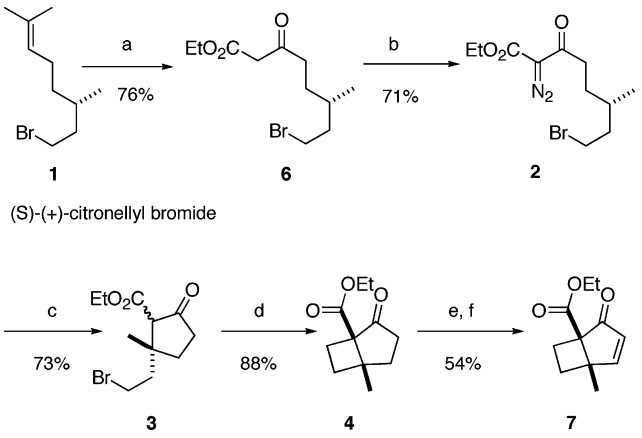
We anticipated that the strain energy in the incipient cyclobutane **4** could make intramolecular alkylation difficult. The literature indicated that solvent, temperature, and base must be chosen judiciously to form cyclobutanes via intramolecular enolate alkylation.[12] In fact, on heating to reflux with K_2CO_3 and NaI in acetone, **3** smoothly cyclized to form the bicycle **4** containing the two chiral quaternary centers of (+)-sulcatine G. For this particular system, the application of halide as the leaving group appeared to us to be critical. Attempted cyclization of the benzenesulfonate analogue of **3** failed.

SCHEME 2. Preparation of Enone 7[a]



[a] (a) O_3, CH_2Cl_2, −78 °C; −78 to 0 °C; $SnCl_2$ (1.2 equiv); N_2CHCO_2Et (1.5 equiv), 3 h; then $KF{\cdot}H_2O$; (b) Et_3N (2.0 equiv), MsN_3 (2.0 equiv), CH_2Cl_2; (c) Rh_2Oct_4 (0.7 mol %), CH_2Cl_2; (d) K_2CO_3 (3.0 equiv), NaI (0.2 equiv), acetone, reflux, 3 h; (e) DMAP·HBr·Br_2, AcOH, room temperature, 2 h; (f) $CaCO_3$, DMF, reflux, 0.5 h.

Pd-mediated conditions[13] for forming the enone **7** from the bicyclic ketone **4** proceeded in low yield and/or with substantial side reactions. We therefore opted for enone formation by dehydrobromination of the monobromo ketone. After attempting some of the standard reagents (*N*-bromosuccinimide, molecular bromine, cupric bromide), a satisfactory yield of the monobromo ketone was obtained using 4-(dimethylamino)pyridinium bromide perbromide in acetic acid.[14] Dehydrobromination with calcium carbonate in hot DMF[15] proceeded smoothly to give the enone **7**.

Construction of the Tricyclic Ester 13. We envisioned using the enone **7** to construct the third ring of sulcatine G (Scheme 3) by, conceptually, conjugate addition followed by intramolecular alkylation. We anticipated that conjugate addition would proceed by selective addition to the exo face of the bicyclic enone. In fact, both bonds were formed in a single step with high diastereocontrol using the Trost annulation.[16]

(4) For leading references to work by others on cyclopentane construction by Rh-mediated intramolecular C−H insertion, see: (a) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (b) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732. (c) Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637. (d) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283. (e) Monteiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 3459. (f) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605. (g) Corey, E. J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995. (h) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 311. (i) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 7065. (j) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (k) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853. (l) Srikrishna, A.; Ravi Kumar, P.; Gharpure, S. J. *Tetrahedron Lett.* **2001**, *42*, 3929. (m) Barberis, M.; Perez-Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* **2001**, *3*, 3317. (n) Dayoub, W.; Diab, Y.; Doutheau, A. *Tetrahedron Lett.* **2002**, *43*, 4131. (o) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887. (p) Sengupta, S.; Mondal, S. *Tetrahedron Lett.* **2003**, *44*, 6405. (q) Chiu, P.; Zhang, X.; Ko, R. Y. Y. *Tetrahedron Lett.* **2004**, *45*, 1531. (r) Pattenden, G.; Blake, A. J.; Constandinos, L. *Tetrahedron Lett.* **2005**, *46*, 1913.

(5) For representative examples of each class of natural products, other than sulcatine G, containing cyclobutanes with adjacent chiral quaternary carbons, see: (a) Solanoeclepin A: Schenk, H.; Driessen, R. A. J.; de Gelder, R.; Goubitz, K.; Nieboer, H.; Bruggemann-Rotgans, I. E. M.; Diepenhorst, P. *Croat. Chem. Acta* **1999**, *72*, 593. (b) Strophanolloside: Kubelka, W.; Kopp, B.; Jentzsch, K. *Pharm. Acta Helv.* **1975**, *50*, 353. (c) Solanascone: Fujimori, T.; Kasuga, R.; Kaneko, H.; Sakamura, S.; Noguchi, M.; Furusaki, A.; Hashiba, N.; Matsumoto, T. *Chem. Commun.* **1978**, 563. (d) 12-*O*-Palmitoyl-4-deoxy-16-hydroxylumiphorbol 13-acetate: Hiroto, M.; Ohigashi, H.; Koshimizu, K. *Agric. Biol. Chem.* **1979**, *43*, 2523. (e) 3-Debromoperforatone: González, A. G.; Aguiar, J. M.; Martín, J. D.; Norte, M. *Tetrahedron Lett.* **1975**, 2499. (f) 2-Isopropylidene-3b,6a-dimethyl-octahydro-cyclobutadicyclopenten-1-one: Bozhkova, N. V.; Stoev, G.; Orahovats, A. S.; Rizov, N. A. *Phytochemistry* **1984**, *23*, 917. (g) Balearone: Amico, V.; Cunsolo, F.; Piattelli, M. *Tetrahedron* **1984**, *40*, 1721. (h) 6β-Acetoxy-13α-hydroxyhaplopan-7-one: Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, *30*, 3683. (i) Tokinolide A: Tsuchida, T.; Kobayashi, M.; Kaneko, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1987**, *35*, 4460. (j) Artelein: Mallabaev, A.; Tashkhodzhaev, B.; Saitbaeva, I. M.; Yagudaev, M. R.; Sidyakin, G. P. *Khim. Prir. Soedin.* **1986**, 46. (k) Lintenone: Fattorusso, E.; Lanzotti, V.; Magno, S.; Mayol, L.; Pansini, M. *J. Org. Chem.* **1992**, *57*, 6921. (l) Maoecrystal M: Shen, X.; Isogai, A.; Furihata, K.; Sun, H.; Suzuki, A. *Phytochemistry* **1994**, *35*, 725. (m) (−)-α-Copaene: Semmler, F. W.; Stenzel, H. *Ber.* **1914**, *47*, 2555. (n) 12-Acetoxyjungistueb-4-en-3-one: Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1983**, *22*, 1201. (o) Vielanin B: Kamperdick, C.; Phuong, N. M.; Van Sung, T.; Adam, G. *Phytochemistry* **2001**, *56*, 335.

(6) Orahovats, A. S.; Bozhkova, N. V.; Hilpert, H. *Tetrahedron Lett.* **1983**, *24*, 947.

(7) Resek, J. E.; Meyers, A. I. *Synlett* **1995**, *2*, 145.

(8) (a) Hue, B. T. B.; Dijkink, J.; Kuiper, S.; Larson, K. K.; Guziec, F. S., Jr.; Goubitz, K.; Fraanje, J.; Schenk, H.; van Maarseveen, J. H.; Hiemstra, H. *Org. Biomol. Chem.* **2003**, *1*, 4364. (b) Benningshof, J. C. J.; Ijsselstijn, M.; Wallner, S. R.; Koster, A. L.; Blaauw, R. H.; van Ginkel, A. E.; Brière, J.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H *J. Chem. Soc., Perkin 1* **2002**, 1701. (c) Benningshof, J. C. J.; Blaauw, R. H.; van Ginkel, A. E.; Brière, J.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin 1* **2002**, 1693. (d) Blaauw, R. H.; Benningshof, J. C. J.; van Ginkel, A. E.; Briere, J.; van Maarseveen, J. H.; Hiemstra, H. *J. Chem. Soc., Perkin 1* **2001**, 2250. (e) Brière, J.; Blaauw, R. H.; Benningshof, J. C. J.; van Ginkel, A. E.; Briere, J.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2001**, 2371. (f) Blaauw, R. H.; Brière, J.; de Jong, R.; Benningshof, J. C. J.; Jorg, C. J.; van Ginkel, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2001**, 66, *233.* (g) Blaauw, R. H.; Brière, J.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Rutjes, F. P. J. T.; Fraanje, J.; Goubitz, K.; Schenk, H.; Hiemstra, H. *Chem. Commun.* **2000**, 1463.

(9) (a) González, A. G.; Darias, J.; Martin, J. D. *Tetrahedron Lett.* **1977**, 3375. (b) González, A. G.; Darias, J.; Martin, J. D.; Melian, M. A. *Tetrahedron Lett.* **1978**, 481.

(10) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1990**, *31*, 4991.

(11) (a) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077. (b) Mesyl azide was prepared according to the reported procedure: Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

(12) (a) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608. (b) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.

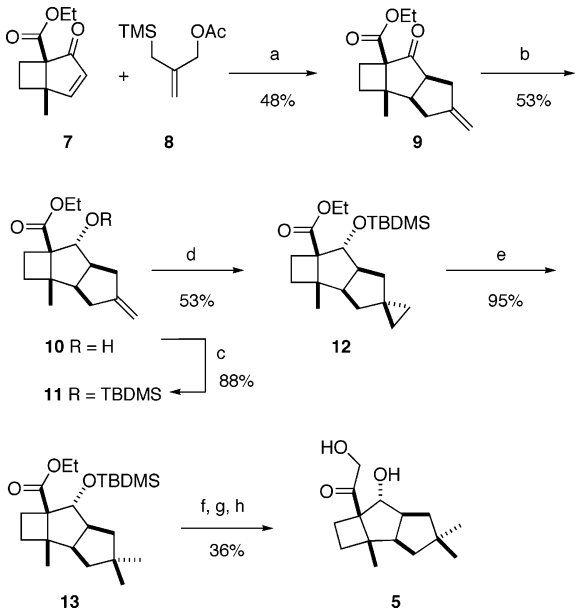
(13) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992.

(14) Arrieta, A.; Ganboa, I.; Palomo, C. *Synth. Commun.* **1984**, *14,* 939.

(15) Green, G.; Long, A. *J. Chem. Soc.* **1961**, 2532.

(16) (a) Trost, B. M.; Chan, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 2315. (b) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284.

SCHEME 3. Synthesis of (+)-Sulcatine G[a]



[a] (a) $Pd(OAc)_2$, $P(OiPr)_3$, BuLi, THF, reflux, 14 h; (b) $NaBH_4$ (3.75 equiv), MeOH, −78 °C to room temperature; HCl(aq); (c) TBDMSCl (1.25 equiv), imidazole (2.50 equiv), DMF; (d) Zn/Cu couple (11.6 equiv), CH_2I_2 (7.6 equiv), ultrasound; (e) PtO_2, acetic acid, sodium acetate, H_2, 40 °C; (f) LDA, MeLi, THF; TESCl; $NaHCO_3$; (g) *m*-CPBA, CH_2Cl_2, 0 °C; (h) TBAF, THF, 0.5 h.

Prior to transforming the olefin to the necessary *gem*-dimethyl-functionalized cyclopentane, the ketone was reduced with sodium borohydride and protected as the *tert*-butyldimethylsilyl ether. We modified LeGoff's procedure for the cyclopropanation of olefins using a zinc−copper couple[17] by increasing the equivalents of both the reducing agent and of the diiodomethane and by substituting ultrasound irradiation for reflux. With these changes we were able to effect clean conversion of **11** to the tetracycle **12**.

As we approached the hydrogenolytic cleavage[18] of the cyclopropane ring, we were concerned that the activated cyclobutane of **12** might also be susceptible to hydrogenolysis. Our initial conditions (PtO_2, acetic acid, 55 °C) proceeded to give mainly **13** having the expected *gem*-dimethyl signals at δ 31 and δ 32 in the ^{13}C NMR spectrum, matching the values for the natural product. This material was contaminated (GC−MS) with two substantial impurities. One impurity showed the same molecular ion as **13**, corresponding to an alternate hydrogenolytic ring opening. The other impurity showed a molecular ion two mass units higher, corresponding perhaps to hydrogenolysis of both the cyclopropane and the cyclobutane rings. Fortunately, hydrogenolysis of the cyclopropane **12** at 40 °C proceeded to give the *gem*-dimethyl product **13** contaminated with only traces of the undesired hydrogenolysis byproducts.

Synthesis of (+)-Sulcatine G 5. We had thought to convert the ester of the tricycle **13** into the necessary α-hydroxy ketone by oxygenation of an enol ether of the corresponding methyl ketone. As the hindered carbonyl of the ester did not respond to the several modifications of the Tebbe reagent, we turned to the Fehr procedure.[19] The original protocol called for the addition of methylmagnesium chloride to the ester in the presence of lithium diisopropylamide. We found that for the tricyclic ester **13**, methyllithium at ambient temperature gave higher conversion than did methylmagnesium chloride at 35 °C. The methyl ketone was not isolated, but was converted directly to the triethylsilyl enol ether by quenching the enolate generated under the reaction conditions with triethylsilyl chloride.

The triethylsilyl enol ether was converted to the triethylsilyl-protected α-hydroxy ketone by reaction with *m*-CPBA.[20] Deprotection of both silyl ethers with TBAF afforded (+)-sulcatine G **5**. The ^{13}C and ^{1}H NMR spectra and sign of rotation of the synthetic (+)-sulcatine G matched those reported for the isolated natural product.

Conclusion

Strategies for enantiocontrolled polycyclic ring construction, from polyolefin cyclization to the intramolecular Diels−Alder reaction, play an important role in organic synthesis. As the computational methods used in pharmaceutical development have improved, receptor binding analysis has led to many potential new drug targets that are polycyclic. The sequence of enantiospecific C−H insertion followed by intramolecular alkylation outlined here is the first illustration of what we expect will be a general route to enantiomerically pure polycyclic systems.

Experimental Section

***β*-Keto Ester (6).** (*S*)-(+)-Citronellyl bromide (35.0 g, 159.7 mmol) dissolved in 500 mL of CH_2Cl_2 was cooled to −78 °C in an acetone/dry ice bath. Ozone was passed through the solution until a blue color persisted. The solution was purged by bubbling nitrogen through it and then warmed to 0 °C in an ice bath. Tin(II) chloride (37.23 g, 196.4 mmol) was added as a solid. After 5 min, ethyl diazoacetate (28.0 g, 245.4 mmol) was added via an addition funnel at a rate that gave steady, but controlled, nitrogen evolution from the reaction mixture. After 3 h, $KF{\cdot}2H_2O$ (45.0 g, 478.1 mmol) was added as a solid to aid the precipitation of tin salts. After 45 min at 0 °C, the reaction mixture was warmed to room temperature and filtered through a Buchner funnel. The filtrate was evaporated onto silica gel and chromatographed to yield **6** as a yellow-tinted oil (33.8 g, 121. 3 mmol, 76% yield). This product was approximately a 1:1 mixture of keto and enol forms. TLC R_f = 0.42 (26% MTBE/ PE); ^{1}H NMR δ 0.92 (t, J = 6.00 Hz, 3 H), 1.28 (t, J = 7.25 Hz, 3 H), 1.45 (m, 1H), 1.68 (m, 3 H), 1.87 (q, J = 7.50 Hz, 1 H), 2.23 (q, J = 6.5 Hz, 1 H), 2.58 (m, 1H), 3.45 (m, 3 H), 4.19 (q, J = 7.25 Hz, 2H), 12.13 (s, 1H); ^{13}C NMR δ d 14.2, 18.8, 31.1, 31.3, 89.2; u 29.7, 31.8, 32.6, 32.9, 39.7, 40.5, 49.4, 60.0, 61.4, 167.2, 172.7, 178.6, 202.6; IR 2963, 1720, 1652, 1457 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_3Br$: 279.0591, obsd: 279.0596; $[\alpha]_D$ +29.0 (*c* 0.19 g/mL, CH_2Cl_2). Anal. Calcd for $C_{11}H_{19}O_3Br$: C, 47.33; H, 6.99. Found: C, 47.47; H, 7.01.

Cyclopentanone (3). The above ester **6** (5.29 g, 19.0 mmol) dissolved in 50 mL of CH_2Cl_2 was cooled to 0 °C. Triethylamine (4.02 g, 39.8 mmol) in 10 mL of CH_2Cl_2 was added followed by mesyl azide[11] (4.85 g, 40.0 mmol) in 10 mL of CH_2Cl_2. After 15 min, the reaction was warmed to room temperature and stirred for an additional 2 h. The reaction mixture was

(17) LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048.
(18) (a) Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4547. (b) Newham, J. *Chem. Rev.* **1963**, *63*, 123.
(19) (a) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1986**, *69*, 228. (b) Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* **1987**, *70,* 1745.
(20) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

partitioned between 1 N aqueous NaOH and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), evaporated onto silica gel, and chromatographed to yield **2** as a bright yellow oil (4.11 g, 13.5 mmol, 80% based on **6** not recovered). A small amount of starting ester **6** (0.59 g, 2.11 mmol) was also recovered from the chromatography. For **2**: TLC R_f = 0.54 (26% MTBE/PE); ^{1}H NMR δ 0.87 (d, J = 5.75 Hz, 3 H), 1.28 (t, J = 7.25 Hz, 3 H), 1.44 (m, 1 H), 1.65 (m, 3H), 1.85 (q, J = 8.75 Hz, 1 H), 2.80 (m, 2 H), 3.38 (q, J = 7.50 Hz, 2 H), 4.24 (q, J = Hz 7.50, 2 H); ^{13}C NMR δ d 14.5, 18.8, 31.4; u 30.7, 31.8, 37.7, 39.7, 61.4, 161.3, 192.7; IR 2135, 1717, 1684, 1654 cm^{-1}; $[\alpha]_D$ −1.80 (*c* 3.72 g/100 mL, CH_2Cl_2).

The diazo compound **2** (25.1 g, 82.4 mmol) dissolved in 500 mL of CH_2Cl_2 (distilled from CaH, then filtered through anhydrous K_2CO_3) was cooled to 0 °C. Rhodium octanoate dimer (443 mg, 0.576 mmol, 0.7 mol %) was added as a solid. The reaction was allowed to come to room temperature overnight. The reaction mixture was evaporated onto silica gel and chromatographed to yield **3** as a colorless oil (16.6 g, 59.9 mmol, 58% yield from **6** not recovered). The product was again an approximately 1:1 mixture of keto and enol forms. For **3**: TLC R_f = 0.53 (25% MTBE/PE); ^{1}H NMR δ 1.02, 1.18 (two s, total = 3H), 1.30 (dt, J = 4.0, 3.0, 3 H), 1.63 (m, 2 H), 2.20 (m, 4 H), 2.95, 3.0 (two s, total = 0.5 H), 3.26 (dt, J = 11.25 Hz, 5.5, 1 H), 3.43 (t, J = 8.75 Hz, 2 H), 4.21 (q, J = 7.25 Hz, 2 H), 10.90 (s, 0.5 H); ^{13}C NMR δ d 14.1, 14.5, 20.9, 25.2, 27.3, 64.6, 65.3; u 27.6, 27.9, 29.6, 30.9, 33.4, 33.8, 34.3, 35.9, 36.1, 41.6, 44.0, 44.4, 44.6, 45.4, 45.9, 60.1, 61.3, 61.5, 105.9, 168.4, 170.1, 177.1, 211.3; IR 2961, 2873, 1757, 1718 cm^{-1}; HRMS calcd for $C_{11}H_{17}O_3Br$: 276.0361, obsd: 276.0352; $[\alpha]_D$ −11.51 (*c* 6.03 g/100 mL, CH_2Cl_2).

Bicyclic Ketone (4). The β-keto ester **3** (2.76 g, 9.95 mmol) was dissolved in 40 mL of dry acetone (filtered through K_2CO_3 and stored over 4 Å molecular sieve). Anhydrous NaI (0.299 g, 2.00 mmol) and anhydrous K_2CO_3 (4.15 g, 30.0 mmol) were added as solids. The reaction was stirred for 3 h at 60 °C and then cooled to room temperature. The mixture was filtered, and the solid was washed with 2 × 30 mL of acetone. The filtrate was evaporated onto silica gel and chromatographed to yield **4** as a colorless oil (1.73 g, 8.82 mmol, 88% yield). TLC R_f = 0.49 (26% MTBE/ PE); ^{1}H NMR δ 1.24 (t, J = 7.25 Hz, 3 H), 1.27 (s, 3 H), 2.02 (m, 5 H), 2.70 (m, 3 H), 4.17 (m, 2 H); ^{13}C NMR δ d 14.52, 22.82; u 21.34, 28.06, 34.72, 38.5, 49.09, 60.60, 60.99, 169.67, 216.75; IR 2954, 2868, 1733, 1456 cm^{-1}; LRMS (electron impact): M$^+$ = 196(30), 181 (7), 168 (27), 150 (100), 123 (93); HRMS calcd for $C_{11}H_{16}O_3$: 196.1099, obsd: 196.1100; $[\alpha]_D$ +283 (*c* 1.17 g/100 mL, CH_2Cl_2). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.00; H, 8.45.

Enone (7). The bicyclic β-keto ester **4** (3.60 g, 18.3 mmol) was dissolved in 60 mL of glacial acetic acid. 4-(Dimethylamino)pyridinium bromide perbromide (6.31 g, 17.4 mmol) was added as a solid. The reaction was stirred at room temperature for 1.5 h and then partitioned between CH_2Cl_2 and, sequentially, water, saturated aqueous $NaHCO_3$, and water. The organic extract was dried (Na_2SO_4) and concentrated to give 5.20 g of golden brown oil. This crude product was determined to be 95% monobromo ketone by GC−MS and was used without further purification. LRMS (electron impact): M$^+$ = 276 (4), 274 (4), 261 (<1), 246 (3), 230 (33), 195 (84), 149 (100).

The crude monobromo ketone was taken up in 20 mL of dimethylformamide (DMF) (stored over 4 Å molecular sieve) and added to calcium carbonate (13.76 g, 137.0 mmol) in 75 mL of refluxing DMF. The reaction was maintained at reflux for 0.5 h then cooled to room temperature. The reaction mixture was partitioned between water (300 mL) and ethyl ether (3 × 100 mL). The combined organic extracts were partitioned between water and then brine and dried with Na_2SO_4. The dried organic extract was evaporated onto silica gel and chromatographed to yield **7** as a slightly yellow oil (1.90 g, 9.78 mmol, 54% yield from **4**). TLC R_f = 0.32 (25% MTBE/PE); ^{1}H NMR δ 1.25 (t, J = 7.25 Hz, 3 H), 1.28 (s, 3H), 1.75−1.98 (m, 2 H), 2.06−2.18 (m, 1 H), 2.85−2.96 (m, 1 H), 4.14−4.24 (m, 2 H), 6.29 (d, J = 5.25 Hz, 1 H), 7.61 (d, J = 5.75 Hz, 1 H); ^{13}C NMR δ d 14.4, 20.1, 132.8, 169.3; u 19.3, 29.8, 52.0, 59.8, 61.3, 169.6, 206.7; IR 2964, 1738, 1583, 1453 cm^{-1}; LRMS (electron impact): M$^+$ = 194 (7), 179 (16), 166 (64), 151 (26), 137 (20), 121 (100); HRMS calcd for $C_{11}H_{15}O_3$: 195.1018, obsd: 195.1021; $[\alpha]_D$ +81.0 (*c* 2.64 g/100 mL, CH_2Cl_2). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.78; H, 7.45.

Tricyclic Ketone (9). Triisopropyl phosphite (0.811 g, 3.89 mmol) in 5 mL of THF was added via syringe to palladium acetate (0.162 g, 0.722 mmol) already blanketed with nitrogen. The mixture was stirred at room temperature for 5 min, forming a yellow solution. A 2.5 M butyllithium/hexanes solution (0.2 mL, 0.5 mmol) was added via syringe, and the mixture was stirred for an additional 10 min, with the solution remaining bright yellow. A mixture of enone **7** (1.83 g, 9.42 mmol) and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **8** (2.63 g, 14.1 mmol) in 6 mL of THF was added via syringe. The reaction was heated at 60−65 °C overnight. The reaction mixture was evaporated directly onto silica gel and chromatographed to yield **9** as a colorless oil (1.13 g, 4.55 mmol, 48% yield). TLC R_f = 0.49 (25% MTBE/PE); ^{1}H NMR δ 1.22 (s, 3 H), 1.24 (t, J = 7.25 Hz, 3 H), 1.90−2.65 (m, 7 H), 2.78−2.86 (m, 2 H), 3.33 (t, J = 8.25 Hz, 1 H), 4.13−4.21 (m, 2 H), 4.83 (d, J = 17.75 Hz, 2 H); ^{13}C NMR δ d 14.4, 20.1, 52.2, 53.2; u 21.0, 29.9, 33.2, 35.3, 48.4, 61.1, 61.2, 106.5, 150.2, 170.0, 217.4; IR 3073, 1741, 1443, 1366 cm^{-1}; LRMS (electron impact): M$^+$ = 248 (21), 233 (13), 220 (10), 202 (100), 174 (90); HRMS calcd for $C_{15}H_{21}O_3$: 249.1492, obsd: 249.1491; $[\alpha]_D$ +188 (*c* 0.97 g/100 mL, CH_2Cl_2).

Alcohol (10). The tricyclic ketone **9** (280 mg, 1.13 mmol) was dissolved in 5 mL of methanol and cooled to −78 °C. Sodium borohydride (161 mg, 4.25 mmol) was added as a solid. The reaction was stirred at this temperature for 0.5 h and then at room temperature for 20 min. The reaction mixture was poured into a mixture of ice (30 mL), 3 N aqueous HCl (25 mL), and ethyl ether (30 mL). The aqueous was extracted with 2 × 50 mL ether. The organic extract was dried with Na_2SO_4. The organic extract was evaporated onto silica gel and chromatographed to yield **10** as a colorless oil (151 mg, 0.601 mmol, 53% yield). TLC R_f = 0.14 (26% MTBE/PE); ^{1}H NMR δ 1.07 (s, 3 H), 1.28 (t, J = 7.25 Hz, 3 H), 1.82−1.89 (m, 2 H), 2.08−2.43 (m, 5 H), 2.57 (bs, 1 H), 2.68−2.72 (m, 3 H), 4.17 (dq, J = 2.5, 7.25 Hz, 2 H), 4.35 (d, J = 9.5 Hz, 1 H), 4.91 (d, J = 2 Hz, 2 H); ^{13}C NMR δ d 14.6, 21.0, 49.7, 54.4, 80.2; u 14.8, 31.5, 35.4, 35.6, 50.4, 59.4, 60.7, 107.3, 151.7, 175.0; IR 1723, 1443, 1367, 1330 cm^{-1}; LRMS (electron impact): M$^+$ = 250 (1), 232 (14), 204 (40), 175 (56), 159 (100); HRMS calcd for $C_{15}H_{23}O_3$: 251.1647, obsd: 251.1646; $[\alpha]_D$ −27.1 (*c* 2.02 g/100 mL, CH_2Cl_2).

***tert*-Butyldimethylsilyl Ether (11).** The alcohol **10** (150.5 mg, 0.601 mmol) was dissolved in 0.25 mL of DMF. *tert*-Butyldimethylsilyl chloride (113.0 mg, 0.751 mmol) followed by imidazole (102.0 mg, 1.50 mmol) were added. The reaction was stirred at 38 °C overnight. The reaction was partitioned between aqueous HCl (1 N, 50 mL) and ethyl ether (30 mL). The organic extract was dried with Na_2SO_4, evaporated onto silica gel, and chromatographed to yield **11** as a colorless oil (193 mg, 0.528 mmol, 88%). TLC R_f = 0.69 (16% MTBE/PE); ^{1}H NMR δ −0.20 (s, 3 H), −0.07 (s, 3 H), 0.77 (s, 9 H), 0.95 (s, 3 H), 1.21 (t, J = 7.25 Hz), 1.65−1.76 (m, 2 H), 1.92−2.67 (m, 8 H), 4.00−4.15 (m, 2 H), 4.32 (d, J = 9.0 Hz, 1 H), 4.83 (d, J = 2.0 Hz, 2 H); ^{13}C NMR δ d −4.6, −4.4, 14.7, 20.9, 25.9, 51.3, 54.3, 81.2; u 14.2, 18.2, 31.3, 50.8, 60.0, 60.5, 107.1, 152.0, 174.7; IR 3071, 2855, 1726, 1659 cm^{-1}; LRMS (electron impact): (m − 15) = 349 (1), 319 (1), 307 (100), 279 (13); HRMS calcd for $C_{21}H_{37}O_3Si$: 365.2512, obsd: 365.2518; $[\alpha]_D$ −4.58 (*c* 1.75 g/100 mL, CH_2Cl_2).

Cyclopropane (12). The zinc/copper couple was prepared by heating cupric acetate (127.0 mg, 0.68 mmol) dissolved in glacial acetic acid (5 mL) to 110 °C. Zinc metal (20 mesh, 1.30

g, 20.0 mmol) was stirred for 2 min in the hot cupric acetate solution. The acetic acid was removed by pipet. While maintaining the temperature at 110 °C, we washed the couple with acetic acid (2 × 3 mL). The couple was cooled to room temperature and then washed with ethyl ether (3 × 15 mL). To the couple under a nitrogen atmosphere was added diiodomethane (1.75 g, 6.53 mmol) in 2.5 mL of ether. The mixture was sonicated in an ultrasound cleaning bath for 5 min. A solution of diiodomethane (1.75 g, 6.53 mmol) and alkene **11** (0.628 g, 1.72 mmol) in 10 mL of ether was added to the activated couple. The reaction was sonicated for 10 h and then partitioned between ice (50 mL), 3 N aqueous HCl (20 mL), and ether (50 mL). After 15 min, the ice had melted and the aqueous was further extracted with ether (2 × 25 mL). The organic extract was dried with Na_2SO_4 and then evaporated onto silica gel and chromatographed to yield **12** as a light yellow oil (346 mg, 0.913 mmol, 53% yield). TLC R_f = 0.51 (5% MTBE/PE); ^{1}H NMR δ −0.11 (s, 3 H), 0.01 (s, 3 H), 0.06 (s, 9 H), 0.30−0.43 (m, 2 H), 0.48−0.59 (m, 2 H), 0.82 (s, 3 H), 1.28 (t, J = 7.25 Hz, 3 H), 1.64−1.91 (m, 6 H), 2.09−2.21 (m, 2 H), 2.30−2.42 (m, 1 H), 2.69−2.77 (q, J = 8.0 Hz, 1 H), 4.08−4.22 (m, 2 H), 4.67 (d J = 8.75 Hz, 1 H); ^{13}C NMR δ d −4.5, −4.3, 14.7, 20.9, 26.0, 52.9, 55.4, 82.4; u 13.2, 14.3, 15.1, 18.2, 21.7, 31.6, 38.5, 39.4, 50.9, 60.1, 60.4, 174.9; IR 3066, 2857, 1726, 1462 cm^{-1}; LRMS (electron impact): (m − 15) = 363 (1), 349 (<1), 333 (1), 321 (100); HRMS calcd for $C_{22}H_{37}O_3Si$: 377.2512, obsd: 377.2502; $[\alpha]_D$ +19.5 (*c* 1.31 g/100 mL, CH_2Cl_2).

***gem*-Dimethyl Cyclopentane (13).** The cyclopropane **12** (141 mg, 0.373 mmol) was dissolved in 1 mL of glacial acetic acid. Sodium acetate (100 mg, 1.22 mmol) and platinum oxide (30 mg, 0.132 mmol) were added as solids. The reaction was stirred under a hydrogen atmosphere at 40 °C overnight. After cooling to room temperature, the reaction was partitioned between water (10 mL) and ether (30 mL). The aqueous layer was twice more extracted with ether (25 mL). The organic extracts were combined and washed consecutively with saturated sodium bicarbonate, water, and brine. The organic extract was dried with Na_2SO_4, evaporated onto silica gel, and chromatographed to yield **13** as a yellow oil (135 mg, 0.355 mmol, 95% yield). TLC R_f = 0.67 (8% MTBE/PE); ^{1}H NMR δ −0.11 (s, 3 H), 0.01 (s, 3 H), 0.83 (s, 9 H), 0.96 (s, 3 H), 0.98 (s, 3 H), 1.14 (s, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.29−1.34 (m, 2 H), 1.55−1.81 (m, 4 H), 2.01−2.14 (m, 2 H), 2.27−2.40 (m, 1 H), 2.58−2.67 (m, 1 H), 4.09−4.21 (m, 2 H), 4.50 (d, J = 8.75 Hz, 1 H); ^{13}C NMR δ d −4.5, −4.3, 14.7, 21.0, 26.0, 31.2, 32.2, 52.3, 54.8, 84.4; u 14.3, 18.2, 31.8, 40.3, 44.3, 44.8, 50.9, 60.0, 60.4, 174.9; IR 1725, 1710, 1658, 1641 cm^{-1}; LRMS (electron impact): (m − 15) = 367 (1), 337 (1), 325 (100), 297 (9); HRMS calcd for $C_{18}H_{31}O_3Si$: 323.2042, obsd: 323.2042; $[\alpha]_D$ +30.76 (*c* 1.50 g/100 mL, CH_2Cl_2).

(+)-Sulcatine G (5). The tricyclic ester **13** (139 mg, 0.366 mmol) was added as a 0.24 M THF solution (1.5 mL of THF) to a −78 °C solution of diisopropylamine (361 mg, 3.57 mmol) and methyllithium (0.5 mL of a 1.6 M ethereal solution, 0.8 mmol) in 2.0 mL of THF. The solution was warmed to approximately 0 °C. Methyllithium (4.9 mL of a 1.6 M ethereal solution, 7.8 mmol) was added via syringe. After being stirred at 0 °C to room temperature for 40 min, the reaction was cooled to −78 °C. Triethylsilyl chloride (1.51 g, 10.0 mmol) in 1.0 mL of THF was added, and the reaction was stirred for 10 min and then warmed to room temperature. Excess base was quenched with saturated $NaHCO_3$ (30 mL), and the mixture was extracted with ether. The organic extract was dried with Na_2SO_4 and concentrated to yield a yellow oil containing the crude enol ether (1.22 g). TLC R_f = 0.84 (2% MTBE/PE); LRMS (electron impact): M^+ = 464 (16), 449 (51), 437 (6), 407 (100).

The crude enol ether (1.22 g, 0.366 mmol theoretical) was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. $NaHCO_3$ (0.500 g, 5.95 mmol) and 3-chloroperoxybenzoic acid (*m*-CPBA) (400 mg of 77%, 1.79 mmol) were added, and the reaction was stirred for 40 min. Excess *m*-CPBA was quenched with saturated aqueous sodium bisulfite (30 mL), and the reaction mixture was partitioned between saturated $NaHCO_3$ (40 mL) and ether (50 mL). The organic extract was dried (Na_2SO_4), evaporated onto silica gel, and chromatographed to yield the impure bis silyl ether as a golden oil (342 mg). TLC R_f = 0.49 (2% MTBE/PE; ^{1}H NMR δ −0.10 (s, 3 H), 0.03 (s, 3 H), 0.65 (q, J = 8.0 Hz, 6 H), 0.83 (s, 9 H), 0.94 (s, 3 H), 0.96 (t, J = 6.0 Hz, 9 H), 0.98 (s, 3 H), 1.13 (s, 3 H), 1.13−1.82 (m, 9 H), 2.13−2.28 (m, 3 H), 2.62 (q, J = 7.25 Hz, 1 H), 3.47 (q, J = 6.75 Hz, 1 H), 4.31 (t, J = 14.75 Hz, 1 H), 4.55 (d, J = 18.0 Hz, 1 H); ^{13}C NMR δ d −4.5, −3.9, 7.0, 21.5, 26.0, 30.9, 31.9, 51.9, 55.6, 85.6; u 4.7, 14.5, 18.2, 29.9, 32.1, 40.5, 44.0, 45.3, 52.0, 64.7, 69.3, 209.6; LRMS (electron impact) M^+ = 480 (1), 465 (1), 451 (36), 291 (100); HRMS calcd for $C_{25}H_{47}O_3Si_2$: 451.3064, obsd: 451.3053.

Silyl-protected sulcatine G (342 mg, 0.366 mmol theoretical) was mixed with solid ammonium chloride (300 mg). A THF solution of tetrabutylammonium fluoride (1.0 M, 1.50 mL, 1.50 mmol) was added, and the mixture was stirred for 1 h. The reaction was diluted with 1 N HCl (30 mL) and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), evaporated onto silica gel, and chromatographed to yield sulcatine G **5** as a colorless oil (33.8 mg, 0.134 mmol, 37% yield overall from **13**). TLC R_f = 0.40 (1:1 ethyl acetate/hexanes), 0.30 (15:1 CH_2Cl_2/methanol); ^{1}H NMR (acetone-d_6) δ 0.95 (s, 3H), 0.98 (s, 3 H), 1.15 (s, 3 H), 1.35 (d, J = 1.0 Hz, 1 H), 1.39 (d, J = 4.0 Hz, 1 H), 1.69 (d, J = 2.25 Hz, 1 H), 1.75 (d, J = 7.5 Hz, 1 H), 1.83 (m, 2 H), 2.21 (m, 3 H), 2.69 (m, 1 H), 3.59 (t, J = 5.0 Hz, 1 H), 4.10 (d, J = 5.5 Hz, 1 H), 4.21 (dd, J = 14.25, 4.75 Hz, 1 H), 4.25 (d, J = 5.0 Hz, 1 H), 4.49 (dd, J = 18.75, 5.0 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ d 21.2, 31.2, 32.1, 51.6, 55.7, 84.5; u 14.4, 32.4, 40.9, 44.8, 45.1, 52.2, 64.3, 68.4, 212.9; LRMS (CI, ammonia): (M^+) = 252 (3), 235 (29), 221 (100), 203 (21), 193 (33); HRMS calcd for $C_{15}H_{23}O_2$: 235.1698, obsd: 235.1694; $[\alpha]_D$ +59.7 (*c* 1.51 $CHCl_3$), lit. $[\alpha]_D$ +44.5 (*c* 0.15 $CHCl_3$).

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds and for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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